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

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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.[1–3] The ischemic penumbra is functionally impaired yet still viable tissue surrounding the ischemic core.[4,5] 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.[4] Alternatively, the penumbra has been defined simply as a region of limited blood supply in which metabolism is preserved.[5] 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.[6] 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.[7–9]

The definition of the penumbra is important in selecting patients suitable for therapeutic intervention.[10] 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.[11,12] Preliminary studies have already used this mismatch as a guideline for therapeutic intervention in ischemic stroke within 6 hours, with promising results.[11,13] However, studies investigating the discrimination between potentially salvageable tissue from tissue that would recover spontaneously within the perfusion/diffusion mismatch are scarce.[14] 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)[12,15–17] or the decrease in apparent diffusion coefficient (ADC), which reflects early cytotoxic edema.[12,18,19]

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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 Signa 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 (S_0, *b* factor 0 s/mm^2, neglecting the contribution of the imaging gradients to the diffusion weighting), as well as 3 diffusion-weighted images with diffusion gradients in orthogonal directions: S_x, S_y, and S_z (*b* factor 1000 s/mm^2). 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) 5000/109 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 (derived from Le Bihan et al[20]): $ADC = -[\ln(S_x/S_0)+\ln(S_y/S_0)+\ln(S_z/S_0)]/3b$, where S_i (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 (pulse 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.

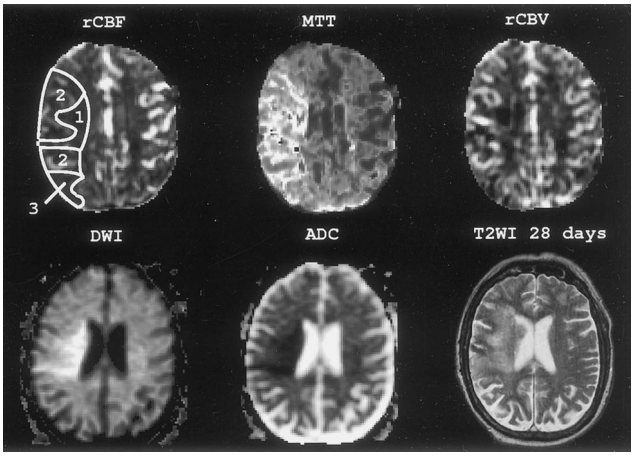

Figure 1. Acute (4-hour) and chronic (28-day) MRI of a 56-year-old man who presented with left hemiparesis, facial paresis, and gaze palsy. Three ROIs were placed manually at the rCBF map (top left): ROI 1 covered the ischemic core as detected from the DWI (bottom left), ROI 2 covered the penumbra that progressed to infarction at the final T2-weighted image (T2WI, bottom right), and ROI 3 covered the penumbra that recovered. Maps of MTT (top middle) showed prolonged MTT in the total right middle cerebral artery territory, whereas rCBV (top right) was markedly reduced in the internal capsule but only mildly reduced in the rest of the middle cerebral artery territory. The ADC map (bottom middle) demonstrates severely reduced ADC in the core of the infarction.

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.[3] 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.

TABLE 1. Clinical Assessment and Infarct Volume of 11 Patients With Acute Stroke

					Lesion Volume/cm^3				Time After Presenting to MRI	
Patient	Age, y	Sex	Presenting Symptom	Location	ROI 1	ROI 2	ROI 3	T2W*	Initial, h	Follow-Up, d
1	50	F	Right hemiparesis and Broca's aphasia	L BG	6.6	1.9	80.0	8.0	4	39
2	54	F	Left hemiparesis and hemineglect	R P+A W	0.5	2.0	111.7	2.0	6	30
3	59	M	Left facial paresis	R MCA	10.8	93.4	55.5	100.6	5	26
4	52	F	Right hemiparesis and aphasia	L BG/IC	7.2	10.4	151.4	16.7	6	21
5	82	F	Left hemiparesis	R BG/IC	15.1	7.3	17.5	22.4	4	25
6	56	M	Left hemiparesis	R MCA	72.6	49.6	112.2	132.0	4	28
7	77	F	Right hemiparesis and Broca's aphasia	L MCA	1.8	0.9	19.4	2.8	5	20
8	59	M	Left hemiparesis	R P+A W	4.4	3.5	120.0	6.7	5	23
9	85	F	Dysarthria and right facial paresis	L MCA	0.6	0.6	20.2	1.1	4	23
10	73	F	Right hemiparesis and aphasia	L MCA	1.4	2.1	116.3	3.4	5	38
11	88	M	Right hemiparesis	L BG/IC	4.7	14.1	17.4	18.1	5.5	31

T2W indicates T2-weighted imaging; F, female; M, male; L, left; R, right; A, anterior; P, posterior; W, watershed area; BG, basal ganglia; IC, internal capsule; and MCA, middle cerebral artery area.

*After 1 month.

Statistical Analysis

Two-way ANOVA was used to compare mean ratios within the ROIs of the 11 patients. Comparisons between the ROIs were performed by paired *t* test, with the Bonferroni correction for multiple tests on the same sample. Receiver operating characteristic (ROC) curves were used to define the optimal cutoff ratio, which was chosen as the ratio that resulted in the highest possible sensitivity and specificity. ROC curves were also used to compare the performance of rCBF, rCBV, and MTT ratios in terms of predicting viable and nonviable tissue by comparison of the areas with Wilcoxon statistics.[25] A multivariate (rCBF ratio, rCBV ratio, and MTT ratio) discriminant analysis was performed to obtain a cutoff function.

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 $0.5 \cdot \text{sensitivity} + 0.5 \cdot \text{specificity}$).[26]

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 rCBV 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 rCBV 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[25] showed that only the difference

TABLE 2. Mean ratios of the 3 ROIs Determined From Maps of rCBF, rCBV, MTT, and ADC

	ROI 1 (Ischemic Core)	ROI 2 (Penumbra→Infarction)	ROI 3 (Penumbra→Recovery)	*P* (ANOVA)
rCBF	0.26±0.11	0.42±0.14	0.62±0.14	<0.001
rCBV	0.55±0.18	0.84±0.23	0.94±0.17	<0.001
MTT	2.53±0.88	2.19±0.72	1.66±0.41	<0.001
ADC	0.62±0.08	0.89±0.13	0.93±0.10	<0.001

Values are mean±SD. The ratio is determined as signal intensity between the ROI on the lesion side related to the contralateral mirror ROI in the healthy hemisphere.

TABLE 3. Cutoff Values of rCBF, rCBV, and MTT Ratios

Parameter	Cutoff Value	Penumbra→Infarct (Sensitivity)	Penumbra→Recovery (Specificity)	Accuracy
rCBF ratio	0.59	0.91	0.73	0.82
rCBV ratio	0.85	0.64	0.73	0.68
MTT ratio	1.63	0.73	0.64	0.68
All	...	0.91	0.73	0.82

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.

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

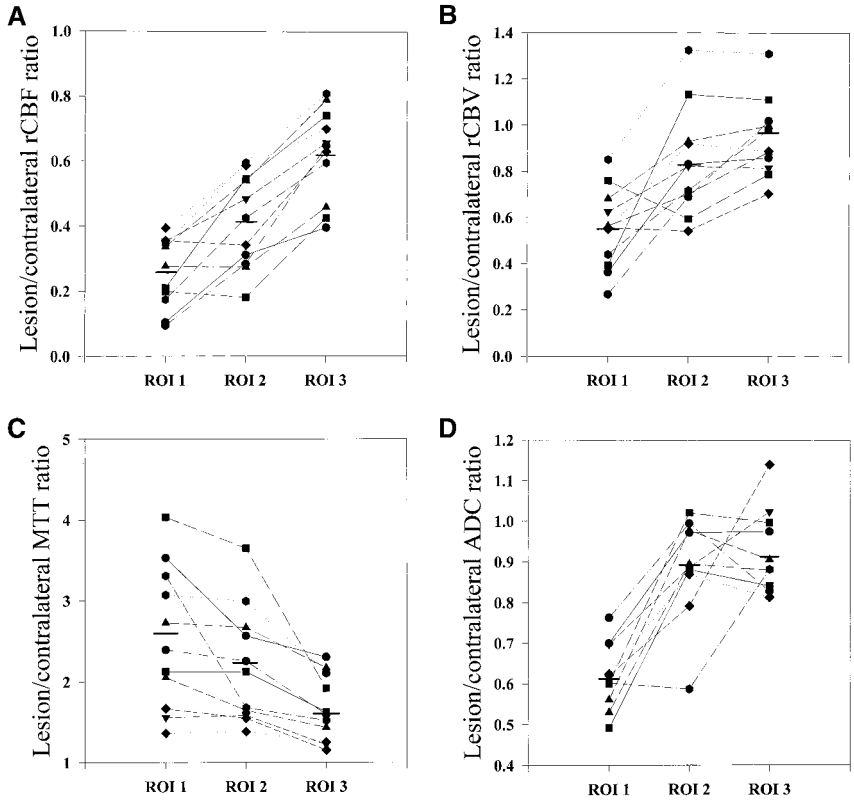

Figure 2. Lesion/contralateral ratios and mean values of ROI 1 (the ischemic core), ROI 2 (the penumbra that progresses to infarction), and ROI 3 (the penumbra that recovers). Ratios of each patient are connected with lines. The rCBF ratio (A) and the rCBV ratio (B) increased from ROI 1 to ROI 3, whereas the MTT ratio (C) decreased. The ADC ratio (D) also showed a tendency to increase; however, there was only a slight rise from ROI 2 to ROI 3.

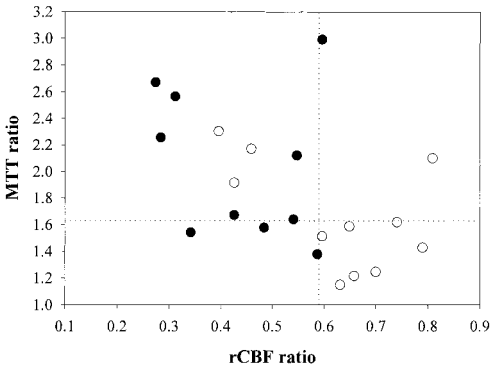

Figure 3. rCBF ratios plotted against the MTT ratios of the penumbra that progressed to infarction (filled circles) and the penumbra that recovered (open circles). The cutoff ratios for the rCBF and the MTT ratios are shown.

the 2 parts of the penumbra than rCBV and MTT, because the accuracy, derived from ROC curves, was higher. Analysis of the areas under the ROC curves was also in favor of the rCBF ratio. The multivariate discriminant analysis including all hemodynamic parameters did not improve the sensitivity or accuracy.

Our results are in accord with similar human studies on CBF thresholds that used PET, single-photon emission CT (SPECT), and functional MRI as well as with experimental studies. Shimosegawa et al[16] performed SPECT on patients within 6 hours of onset of stroke and found mean CBF ratios for infarct and peri-infarct regions to be 0.48 and 0.75, respectively. Because follow-up CT was used in their study for morphological changes, the infarct area in the hyperacute phase could not be detected. Thus, the infarct region was a mixture of the core and penumbra progressing to infarction, and consequently, their mean ratios are somewhat higher. Using PWI and DWI, Schlaug et al[12] found the mean rCBF ratio in the core and the penumbra (operationally defined as tissue that later went on to infarction) to be 0.11 and 0.37, respectively, in rough agreement with our results (0.26 and 0.42, respectively).

In a rat model of stroke, Hoehn-Berlage et al[18] found absolute CBF thresholds at 2 hours after the infarct of the core (18 mL/100 g per minute) and the penumbra (31 mL/100 g per minute). By using the mean value of CBF for mixed gray/white matter in humans (50 mL/100 g per minute),[27] our mean ratios of the core and the penumbra progressing to infarction correspond to 13 and 21 mL/100 g per minute, respectively (Table 2). These small discrepancies between their values and ours could be due to differences between species.

Using the stable xenon CT technique[28] or PET,[29] others have found very low absolute CBF thresholds for irreversible damage (from 6 to 8.43 mL/100 mL per minute). These low values can be explained by longer inclusion periods (from 5 to 18 hours) in 1 study[29] (because ischemic flow thresholds decline with time) and by differences in methodology (steal phenomenon due to CBF increase in nonischemic tissue caused by xenon inhalation) in the other study.[30]

In view of acute stroke management, it is essential to be able to discriminate mildly hypoperfused tissue that recovers spontaneously and more seriously hypoperfused tissue that may escape infarction if treated. Furlan et al[7] found that it was not possible to discriminate between the 2 parts of the penumbra on the basis of CBF levels, as opposed to the present study and the study of Liu et al.[14] According to our findings, the tissue at risk in the penumbra is characterized by an rCBF ratio of less than roughly 0.59.

In ischemic cerebrovascular disease, the initial event is reduction of the cerebral perfusion pressure. Compensatory vasodilation occurs, and the increase of CBV thereby increases the CBV/CBF ratio, ie, the MTT.[31] With further reduction of the perfusion pressure, the limit of cerebral autoregulation is reached as vasodilation becomes maximal and the CBF begins to decrease; finally, CBV also declines, with a gradual collapse of the vessels.[32] Accordingly, as CBF declines, there is a period when CBV is increased. Because of this bimodal behavior, the CBV ratio may be difficult to interpret in terms of prognostic value. This may explain the finding that CBV is a poor predictor of the fate of the operationally defined penumbra found in the present study. With the use of different investigatory methods (PET, SPECT, and PWI), increased CBV in ischemic tissue has been demonstrated in experimental studies[33–35] as well as in human studies.[3,12,15,36–38] 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.[39] In the literature, the prognostic importance of a high CBV is uncertain. In a combined PWI/SPECT study of Hatazawa et al,[15] 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.[12] Accordingly, they concluded that increased rCBV is a predictor of stroke evolution. Finally, Liu et al,[14] 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.[39,40]

We found a longer MTT with more severe ischemia, in accordance with MTT being inversely related to the perfusion pressure.[34,35,37,41,42] This may be because MTT increases monotonically with perfusion pressure even though the CBV changes are bimodal with a decrease in perfusion pressure.[31] MTT is regarded an excellent measure of perfusion pressure[34,35,37,42] and has potential as the parameter from which patients are selected for treatment. This has recently been demonstrated by Sunshine et al,[11] 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 artery 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 al[12] 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 al[45] 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 PWI[15] 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.

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