Does the Mismatch Match the Penumbra?
Magnetic Resonance Imaging and Positron Emission Tomography in Early Ischemic Stroke

Jan Sobesky, MD; Olivier Zaro Weber, MD; Fritz-Georg Lehnhardt, MD; Volker Hesselmann, MD; Michael Neveling, MD; Andreas Jacobs, MD; Wolf-Dieter Heiss, MD

Background and Purpose—In ischemic stroke, diffusion-weighted (DW) and perfusion-weighted (PW) magnet resonance imaging (MRI) is used to define the mismatch as the therapeutic target. With positron emission tomography (PET), we characterized the metabolic patterns of tissue compartments identified by MRI and compared the volumes of mismatch to those of PET-defined penumbra.

Methods—In 6 acute (median, 5.2 hours) and 7 chronic (median, 10 days) stroke patients in whom a mismatch was defined by PW/DW MRI, PET was performed (median, 120-minute delay). Cerebral blood flow (CBF), oxygen metabolism (CMRO₂), and oxygen extraction fraction (OEF) was determined in the areas of DWI lesion, mismatch, and oligemia. Then, the mismatch volume was compared with the volume of penumbra.

Results—DWI lesions showed impaired tissue integrity (low CMRO₂ and low OEF). Mismatch areas were viable (normal CMRO₂) but showed largely varying OEF. Oligemic areas had metabolic patterns comparable to normal tissue. A mismatch volume was found in all 13 patients. However, only 8 of 13 had a corresponding penumbra volume that covered only a part of the mismatch.

Conclusion—Our comparative PET/MRI study confirmed the current pathophysiological hypothesis for the DWI lesion and for the oligemic areas. However, the mismatch area did not reliably detect elevated OEF and overestimated the penumbra defined by PET. (Stroke. 2005;36:980-985.)

Key Words: cerebral blood flow • magnetic resonance imaging • perfusion • stroke, acute • tomography, emission computed

Positron emission tomography (PET) provides detailed insight into the complex pathophysiological changes after cerebral ischemia. Three tissue compartments have been described as the main players in stroke diagnosis and therapy:1–5 (1) the ischemic core that turns into infarction despite successful reperfusion and regardless of cerebral blood flow (CBF); (2) the area of oligemia with preserved neuronal integrity and normal or slightly decreased perfusion that will not turn into infarction unless a repeated and more severe ischemic challenge occurs; and (3) the penumbra,6 ie, the tissue with preserved neuronal integrity but hypoperfused at a level to cause functional impairment. Its hallmark is the elevated oxygen extraction fraction (OEF), reflecting a compensatory mechanism in still viable but threatened tissue.

The increasingly available stroke magnetic resonance imaging (MRI) introduced markers for tissue integrity (diffusion-weighted imaging [DWI]) and for cerebral perfusion (perfusion-weighted imaging [PWI]) into clinical routine7–10 and the concept of “penumbra” has been replaced by the concept of “mismatch.” However, the analogy of mismatch and penumbra is derived from a theoretical concept and has not been substantiated by comparative studies in human stroke. It was the aim of this study to compare PW/DW MRI and PET in individual patients to: (1) define the metabolic signature of various tissue compartments identified by MRI; and (2) compare the volume of mismatch to the volume of penumbra.

Materials and Methods

Subjects
We included 6 acute and 7 chronic ischemic stroke patients presenting a mismatch on MRI. All patients received routine neurological examination, MRI scanning, and standard medical treatment. After informed consent, PET followed under continuous monitoring and surveillance of an experienced stroke neurologist. No change of the neurological status was observed between the imaging studies. The study was approved by the local ethics committee.
Imaging

MRI was performed on a 1.5-T Scanner (Philips Intera Master). For DWI (b = 0 and b = 1000 s/mm²), 3 gradients were applied and the isotropic image was calculated (echo time of 96 ms, repetition time of 3560 ms, a matrix size of 128 × 128, field of view 230 × 230 mm). PW images were assessed in axial direction (20 slices, 6-mm slice thickness, 0.6-mm interslice gap, field of view 23 cm) using multi-shot 3-dimensional T2*-weighted gradient echo EPI-PRESTO sequences (repetition time, 17 ms; effective echo time, 25 ms; flip angle 9°, EPI factor, 17; matrix, 64 × 51; resulting voxel size, 3.6 × 3.6 × 6 mm). PWI was assessed by 60 measurements at intervals of 1.3 seconds after intravenous injection of 20 mL gadolinium-dTPA (Magnavist, Schering AG) with a flow rate of 10 mL/s.

PET studies were performed in a resting state on an ECAT EXACT HR Scanner (Siemens/CTI) in a 3-dimensional data acquisition mode providing 47 contiguous 3-mm slices of 5-mm full-width half-maximum in-plane reconstructed resolution. CBF was measured according to the ¹⁵O-water intravenous bolus method with 20 mCi. Then, the patient inhaled ¹⁵O₂ gas (50 mCi) in a deep single breath. The cerebral blood volume was estimated (4 mL/100 g). With arterial blood sampling from a radial artery catheter, the regional values for CBF, CMRO₂, and OEF were calculated. The cerebral metabolic rate for oxygen (CMRO₂) was calculated from PET images of ¹⁵O-water and arterial blood samples, assuming an arterial oxygen content (Cao₂) of 200 mL%. The relative OEF was calculated as 1 - CBF × Cao₂ / CMRO₂. The CBF, CMRO₂, and OEF were then averaged over the region of interest (ROI) covering the contralateral MCA territory.

Postprocessing

PET and time-to-peak (TTP) images were coregistered by an automatic matching routine and resized to the same voxel size. For DWI, the isotropic images (b = 1000 s/mm²) were used for further analysis and the voxel values were expressed as a ratio compared with the mean voxel value of a region of interest (ROI) covering the contralateral MCA territory. For PWI, the TTP maps were calculated as previously described, and the relative TTP delay was used for further analysis. PET data were expressed as absolute values.

Clinical Patient Data

<table>
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<th>ID</th>
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<th>Time Onset of Symptom Imaging, d/h</th>
<th>Time MRI to PET, min</th>
<th>NIHSS, No.</th>
<th>DWI Lesion Volume, cm³</th>
<th>Mismatch Volume TTP &gt;4 cm³</th>
<th>Mismatch Volume TTP &gt;6 cm³</th>
<th>Penumbra Volume, cm³</th>
<th>Site of Ischemia</th>
<th>Vessel Pathology/Degree of Stenosis, %</th>
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<td>46.2</td>
<td>80.6</td>
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<td>80</td>
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<td>R/MCA</td>
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ACA indicates anterior cerebral artery; ICA, internal carotid artery; F, female; L; left; M, male; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; R, right.

Figure 1. Coregistered images of PW/DW MRI and multitracer PET in a patient with an acute right-side hemiparesis. The ROIs were placed according to the MRI criteria (see Materials and Methods section) and then transferred to the PET images (ROI colors: red indicates DWI lesion; blue, mismatch; yellow, oligemia; green, reference region).
5 to 30) of stroke. The median time delay between MRI and PET was 120 minutes (range, 60 to 270 minutes). DWI lesions were found in 8 of 13 patients (median volume, 16 cm³; range, 8.2 to 101 cm³). Patients measured in the acute and subacute phase did not differ significantly in age, time delay between MRI and PET, National Institutes of Health Stroke Scale score or DWI lesion volume. In 2 patients, the stroke was classified as embolic (patients 2 and 5). The other cases were classified as hemodynamic strokes.

For part A, in the ROI-based analysis (131 cortical ROIs), the median values for DWI lesion, mismatch, oligemia, and reference tissue were as follows (Figure 2), for CBF: 17.5, 34.2, 44.1, and 51.7 mL/100 grams per minute; for CMRO₂: 32.6, 128.0, 145.7, and 156.1 μmol/100 grams per minute; for OEF: 13.1, 49.5, 42.8, and 38.1%. PET values in acute and chronic imaging only differed significantly for CBF and CMRO₂ in the reference region (median, 47 versus 59 mL/100 grams per minute and 142 versus 170 μmol/100 grams per minute) and for OEF in the oligemic region (39% versus 42%). The combined analysis of CMRO₂ and OEF values with respect to the tissue compartments in all 13 patients is illustrated in Figure 3.

For part B, the voxel-based volumetric analysis detected a DW/PW MRI mismatch volume for TTP >4 seconds in all 13 patients as illustrated in Figure 4 (median volume, 107.9 cm³; range, 4 to 473). However, in only 8 of 13 patients, the mismatch volume corresponded to a volume of OEF elevation on PET imaging (n=8; median volume, 4.9 cm³; range, 1.3 to 260) (Figure 5). The penumbra was located within the mismatch volume but was smaller and covered 1% to 75% of the mismatch. The volumes of DWI lesion, mismatch, and penumbra did not differ significantly between the patients measured in the acute and chronic phase. If the TTP threshold was increased to TTP >6 seconds, 10 of 13 patients had a mismatch. In 8 of these 10 cases, a penumbra was found. In 1 patient (patient 1), the penumbra was larger than the mismatch. In the remaining 7 patients, the penumbra was smaller and covered 2% to 82% of the mismatch.

Discussion
The concept of penumbra was derived from animal studies, which demonstrated a loss of electrophysiological properties without signs of morphological damage.6 In humans, PET studies reflected this concept in a noninvasive approach. Impaired tissue integrity was reliably identified by a decreased oxygen metabolism16,17 or a decreased binding of 11C-Flumazenil (FMZ),2,15 and thresholds highly predictive for subsequent infarction were established. Acute stroke studies showed that a considerable part of the final infarct has
already lost cellular integrity and is not accessible to therapy even in the early phase.\textsuperscript{1,2} However, PET detected viable but hypoperfused tissue that was characterized by an elevated oxygen extraction fraction and accessible to acute therapy.\textsuperscript{3,18} This pattern, originally labeled “misery perfusion,”\textsuperscript{19} was used as a surrogate marker of penumbra because it surrounds the ischemic core and has a yet undetermined fate.

This PET-based concept was adopted into a broader clinical application by stroke MRI. The volumetric difference of hemodynamically compromised (PWI) but viable (DWI) tissue, the mismatch, is used to estimate the penumbra.\textsuperscript{7,9} Few in vivo data back up this hypothetical link between the 2 different methods. Comparative studies of PWI and CBF have only been performed in healthy volunteers and patients with chronic occlusive disease. The PWI-derived CBF, cerebral blood volume, and mean transit time values obtained by deconvoluting algorithms and correction for interindividual differences correlated with respective PET data in predefined ROIs.\textsuperscript{20–22} For relative TTP maps, a correlation of the TTP delay and decreased perfusion has been described in chronic stroke patients with several days between PET and MRI.\textsuperscript{23} Penumbra and mismatch have not yet been systematically compared in early ischemic stroke and our data may therefore serve to close the gap between previous PET and MRI.
studies. We included patients with a first ischemic hemispheric stroke that showed a mismatch on MRI. Then, the respective metabolic patterns on PET imaging were defined. Because no clinical change was observed between the scans, relevant changes of CBF or metabolism are not probable.

**Metabolic Patterns of the DWI Lesion**
Within the DWI lesion, CMRO$_2$ was significantly decreased (median, 32.6 $\mu$mol/100 grams per minute). The values were $<60$ $\mu$mol/100 grams per minute, which is the threshold for probable infarct development. Likewise, the OEF was decreased (median 13.1%) to values clearly below the normal range. CBF values were low (median 17.5 mL/100 grams per minute) but still within the penumbral range, thus higher than expected for nonviable tissue. These patterns reflect the perfusion-independent breakdown of oxygen metabolism as a marker of irreversible neuronal damage. The finding that parts of the DWI lesion had normal values for CMRO$_2$ and OEF is in line with previous studies and emphasizes the high sensitivity but lower specificity of DWI for infarct prediction.

**Metabolic Patterns of the Mismatch Area**
Relative TTP maps are only indirect surrogates of CBF and do not represent the best performance of DW/PW MRI. However, they are frequently used in clinical routine because they clearly visualize hemodynamic alterations, do not rely on extensive postprocessing, and yield satisfactory results if compared with quantitative methods. A relative TTP delay of $>4$ seconds was used for the mismatch definition because it best defines penumbral flow and correlates to the clinical deficit. In the mismatch area, oxygen metabolism values were above the viability threshold, indicating a preserved neuronal integrity (median 128 $\mu$mol/100 grams per minute). This finding confirms the viability but it does not prove that this tissue is indeed “at risk,” because the definition of penumbra is based on elevated OEF values. The OEF value of the reference region assessed in our patient sample (median, 38.1%) was in line with previous reports. The mismatch area therefore had elevated OEF values (median, 49.5%), pointing at a metabolic compensation in hypoperfused but viable tissue. However, the huge range of the OEF values (27.8% to 71.7%) implied that the label “mismatch area” did not reliably represent areas with elevated OEF. A considerable proportion had normal OEF values and therefore did not meet the criteria of penumbra as defined by PET.

**Metabolic Patterns of the Oligemic Area**
“Oligemia” describes the tissue with only modest hemodynamic compromise. We found a preserved tissue integrity, normal perfusion values, and normal to slightly elevated OEF values (median, 42.8%). According to the pathophysiological concept, the metabolic features were between those of the reference tissue and the mismatch area. This compartment did therefore not meet the criteria of penumbra.

**Mismatch Versus Penumbra**
Using a voxel-based volumetric approach, we found an overestimation of penumbra by the DWI/TTP mismatch that depended on the chosen TTP threshold; in 8 of 13 patients, the mismatch volume (defined by TTP $>4$ seconds) corresponded to a penumbra. If present, the penumbra covered only a part of the mismatch. The use of a higher TTP threshold (ie, TTP $>6$ seconds) approximated the volume of mismatch to the volume of penumbra. However, it did not change the essential of our findings. The TTP thresholds were chosen according to a recent comparative study that showed that TTP $>4$ seconds and TTP $>6$ seconds yield the best estimate of penumbral flow in terms of sensitivity and specificity. Our results were not sufficiently explained by clinical data or by differences between acute and chronic measurements, although a decrease of penumbra over time has to be postulated. Several method-specific differences contribute to this discrepancy: first, the underlying method of flow measurement; the fundamental physiological difference of TTP and CBF imaging results in an increased susceptibility of TTP maps to collateral flow or individually altered hemodynamic properties. The impact of the underlying vessel disease on the penumbra/mismatch ratio cannot be derived from our study but may be substantial. Second, the different definition of the tissue compartments: OEF mainly describes the balance of perfusion (CBF) and metabolism (CMRO$_2$) in a tissue compartment. In contrast, the mismatch definition is based on a “normal” appearance on DWI images and then uses TTP values as the only determinant of the “tissue at risk.” The weak correlation of TTP delay and OEF elevation found in our study ($p=0.52$, $P<0.005$ for oligemic and mismatch area ROIs) is in line with a previous report of chronic stroke patients. Third, the combined analysis of gray and white matter: CBF images better-discriminate high cortical flow values from low values in white matter than TTP images. A combined analysis of these compartments additionally impairs the congruence of TTP delay and OEF elevation.

These important method-specific issues emphasize that our results are based on the aforementioned DWI/TTP method, which is the modality applied most often in clinical routine. The results of this comparison of methods depend on the procedure of analyzing the nonquantitative DW/PW MRI data and may be improved by a more sophisticated analysis. Additionally, the presented conclusions are mainly derived from hemodynamic strokes and summarize different stages of stroke. Further comparative studies will have to define the impact of the underlying stroke pathomechanism, the influence of the time between stroke and imaging, and will help to specify the performance of different PWI parameters for the detection of the penumbra.

**Conclusion**
The metabolic patterns behind MRI-based compartments are defined as follows: (1) with few exceptions, the DWI lesion displayed metabolic features of irreversible tissue loss; (2) the oligemic region was defined by viable tissue not at risk for infarction; (3) the mismatch area had preserved neuronal integrity but showed a largely varying oxygen extraction fraction; and (4) in a volumetric comparison, the DWI/TTP mismatch overestimated the volume of penumbra and therefore the tissue at risk. The results of this study should be
considered in the clinical application of the mismatch concept.

Acknowledgment

We express our gratitude to the members of the neurocritical care unit (Department of Neurology), to the staff of the MRI facility (Department of Neuroradiology), and especially to the staff of the PET unit (Max Planck Institute for Neurological Research) for helpful cooperation in this multimodal imaging study.

References

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Stroke. 2005;36:980-985; originally published online March 24, 2005; doi: 10.1161/01.STR.0000160751.79241.a3
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

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