Identifying Thresholds for Penumbra and Irreversible Tissue Damage

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Abstract—Diffusion-weighted MRI (DWI) in combination with perfusion-weighted MRI (PWI) has become a widely accepted modality for the selection of patients amenable for acute therapy, if a mismatch between these procedures suggests viable penumbral tissue. However, DWI as well as PWI yields semiquantitative measures limiting the definitions of irreversible damage and of potentially viable penumbral tissue. These limitations of PWI/DWI may be better understood if findings in individual patients are compared with the results from measurements of blood flow, oxygen metabolism, and benzodiazepine receptor binding obtained with positron emission tomography (PET). Comparative studies with PET and MRI were performed in 3 groups of patients: (1) In 12 acute stroke patients, results from DWI (median, 6.5 hours after symptom onset) and 11C-flumazenil (FMZ) PET (median, 85 minutes between DWI and PET) were compared with infarct extension 24 to 48 hours later on T2-weighted MRI. (2) In 11 acute stroke patients, results from PWI (median, 8 hours after symptom onset) were compared with cerebral blood flow measurements obtained with [15O]H2O PET (interval, 60 minutes between PWI and PET). (3) In 10 patients with acute (n=5) or chronic stroke (n=5), results from PWI/DWI were compared with PET of cerebral blood flow and oxygen consumption to detect mismatch or increased oxygen extraction fraction as surrogate markers of penumbra. Results were: (1) from regions with increased DWI intensity, decreased apparent diffusion coefficient (ADC) and decreased FMZ binding probability curves were computed for eventual infarction, and 95% prediction limits were determined. These limits predicted 83.5% (FMZ), 84.7% (DWI), and 70.9% (ADC) of the final infarct volume. However, the false-positive predictions were much higher for the DWI variables (5.1 and 3.6 cm3 for DWI and ADC versus a median of 0 for FMZ). (2) The comparison of volumes generated by different time to peak (TTP) thresholds (PWI) and hypoperfusion <20 mL/100 g per minute (PET) indicates that a TTP delay of 4 to 6 seconds yields a fair estimate of hypoperfusion. (3) The PWI/DWI mismatch with TTP >4 seconds did not reliably correspond to the penumbra as assessed by PET (oxygen extraction fraction >150%). Only 6 of 10 patients with a mismatch had areas of penumbral. In these cases, the penumbra volume was overestimated by MRI. DWI correlates with FMZ results and, with a few exceptions, yields a good estimate of acute tissue damage and final infarct volume. PWI measures seem to be less reliable; the TTP prolongation of >4 seconds assessed only 83% of the volume of hypoperfusion <20 mL/100 g per minute. The mismatch volume imprecisely depicts increased oxygen extraction fraction, and, despite its clinical role for selection of patients for eventual therapy, it does not seem to be a reliable correlate of penumbra. (Stroke. 2004;35[suppl I]:2671-2674.)

Key Words: magnetic resonance imaging, diffusion-weighted ▪ magnetic resonance imaging, perfusion-weighted ▪ penumbra ▪ stroke, ischemic ▪ tomography, emission-computed

The concept of penumbra is based on animal experiments in which potentially reversible functional disturbances can be observed when blood flow decreases beyond a critical threshold (review in Heiss1). With reperfusion within a limited time window, these functional disturbances are reversible without leading to morphological damage and irreversible neurological deficits. In the last 20 years, surrogate markers of penumbra and irreversible tissue damage were studied, especially in regard to patients who could benefit from treatment in acute ischemic stroke (reviews in Keir and Wardlaw2 and Donnan and Davis3). Positron emission tomography (PET) has been the gold standard but was replaced by diffusion- (DWI) and perfusion-weighted imaging (PWI) because of its wider distribution and the less complex logistics involved.4,5 However, there are some limitations with conventional DWI/PWI: increased diffusion signals can be reversible,6 and the determination of the threshold of critical perfusion by PWI is still a matter of ongoing debate.7 Therefore, we compared these methods in a limited number of patients with acute ischemic stroke.

Subjects and Methods

Comparative studies with PET and MRI were performed in 3 groups of patients: (1) In 12 acute stroke patients (5 men, 7 women, aged 37 to 74 years; mean age, 62.4 years), DWI was performed 2.7 to 19
hours after symptom onset (median, 6.5 hours) and was followed by PET of $^{15}$O-flumazenil (FMZ) within 20 to 130 minutes (median, 85 minutes). The early imaging findings were compared with infarct extension on T2-weighted MRI 24 to 48 hours later. (2) In 11 acute stroke patients (7 men, 4 women, aged 37 to 78 years; mean age, 56 years), PWI was performed 1.8 to 20 hours after symptom onset (median, 8 hours) and was followed by PET of $[^{15}O]$H$_2$O within 20 to 140 minutes (median, 60 minutes). Increases in time to peak (TTP) maps on PWI were compared with regional cerebral blood flow (CBF) values from PET. (3) In 10 patients with acute (n=5; median, 5 hours after symptom onset) and chronic stroke (n=5; median, 8 days after symptom onset), PWI and DWI were performed and were followed by PET of H$_2$O (for CBF) and of $[^{15}O]$O$_2$ (for oxygen consumption) within 1.5 to 4 hours (median, 2 hours). In these cases, the extent of PWI/DWI mismatch was compared with that of increased oxygen extraction fraction (OEF) as a surrogate marker of penuroma.

All patients included in this study suffered from ischemic hemispheric stroke of different severity, with clinical deficits ranging from mild (and transient) paresis of an arm to severe contralateral sensorimotor deficit (initial National Institutes of Health Stroke Scale score between 1 and 22 points; median, 6 points). Initial assessment included general medical and standardized neurological examinations and CT scanning. The patients received standard medical therapy; 8 patients arriving within the 3-hour window received intravenous thrombolysis before the imaging protocol was started. Fully informed consent was obtained from all patients.

MRI was performed on a Philips Intera 1.5-T whole-body scanner with single-shot and multishot spin-echo-planar imaging sequences providing 20 slices with a thickness of 6 mm. For DWI, 2 b values (b=0 and b=1000 s/mm$^2$) were used, and DWI intensity maps and maps of the apparent diffusion coefficient (ADC) were calculated. The perfusion studies consisted of multiple measurements (40 at 2.6-second intervals or 60 at 1.3-second intervals) after a standardized injection of 20 mL GdDTPA with a flow rate of 10 mL/s. TTP maps were calculated from the raw data with the use of an interactive data language–based interactive program (Research Systems Inc). DWI intensity and ADC values were expressed as a ratio, and TTP values were expressed as the difference from the contralateral homotopic region. Size and location of the final infarct were determined 24 to 48 hours later on T2-weighted MRI. PET studies were performed with the patients in a resting state on an ECAT EXACT HR scanner (Siemens/CTI) in 3-dimensional data acquisition mode, providing 47 contiguous 3-mm slices at 5-mm full width at half maximum reconstructed resolution. As a tracer of neuronal integrity, $^{11}$C-FMZ (740 MBq) was injected intravenously, and ratios of cortical FMZ binding in the affected hemisphere relative to the contralateral white matter activity were assessed. Regional CBF was measured after intravenous bolus injection of $[^{15}O]$H$_2$O (2.2 GBq) with the use of arterial blood sampling. Oxygen consumption was measured after a single-breath inhalation of $[^{15}O]$O$_2$ (1.85 GBq), and the cerebral metabolic rate of oxygen (CMRO$_2$) and OEF were calculated with the use of the arterial input function.

The early PET, DWI, and PWI as well as the late T2-weighted MRI results were individually coregistered by a multimodal coregistration program. For DWI/FMZ comparison, spherical volumes of interest were placed in coregistered images of different variables. Regional values from different modalities were compared among each other or related to the final state, i.e., infarcted or noninfarcted on late MRI. In a second step, the tissue compartments created by various thresholds were compared among the different modalities with the use of voxel-based atlases (Figure 1).

### Results

#### Assessment of Cortical Tissue Damage

In the patients of group 1, cortical areas were categorized as infarction or normal according to their appearance on follow-up MRI, and volumes of interest of 6-mm diameter were fitted into the cortical rim of the coregistered DWI, ADC, and FMZ images. Across all patients’ volumes of interest, the threshold probability integrals of final infarction or noninfarction were interactively computed, and positive prediction curves were obtained on which 95% prediction limits could be defined. These values—FMZ binding 3.2 times the mean of the contralateral white matter, DWI intensity 1.18 times the contralateral area, ADC 0.83 times the mean of the contralateral white matter, and TTP 4.4 compared to the contralateral side—represent the 95% probability threshold of final infarction.

When the volumes of tissue beyond these thresholds were compared, close correlations between volumes with FMZ and DWI beyond threshold as well as between predicted and final infarct volumes were obtained (Figure 2), but the volumes did not correlate perfectly.
not completely overlap. Overall, 83.5% of the final infarct (median, 14.9 cm³) was predicted by decreased FMZ binding, 84.7% by increased DWI signal, and 70.9% by reduced ADC value. However, because of the incongruities, only a small part of the final infarct was not predicted by FMZ or DWI value beyond the critical limit (median, 1.1 cm³). The false-positive rates showed significant differences: only a small part (median, 0; mean, 0.9 cm³) of the finally noninfarcted tissue had initially decreased FMZ binding, whereas 5.1 cm³ of finally normal tissue showed an increased DWI signal (25.9% of the total volume of DWI increase) and 3.6 cm³ showed a decreased ADC value (22.3% of total volume). These differences were significant (P<0.01, Wilcoxon test).

The volumes of infarcted tissue not predicted by decreased FMZ or changed DWI signal were comparable. In single cases, areas with markedly increased DWI signal did not show either impaired FMZ binding or a lesion on late MRI, as reported previously, but in most cases the differences with respect to FMZ binding and DWI signals were at the borderline of the ischemic territory.

### Assessment of Perfusion

PWI-derived TTP maps were compared with quantified PET CBF images to test different TTP thresholds for their ability to identify hypoperfusion. After coregistration of the MR and PET images, an individual brain atlas was created for each patient. Then the volume of hypoperfusion of <20 mL/100 g per minute (PET CBF) was created with the use of a voxel-based threshold function. Within the same brain atlas, the TTP images were analyzed with stepwise increasing thresholds, ie, with increasing relative TTP delays (2, 4, 6, 8, 10 seconds with respect to the unaffected hemisphere). The volume of CBF hypoperfusion ranged from 1.2 to 362 cm³ (median, 34.5 cm³). The voxel-based 3-dimensional fusion of each patient’s hypoperfusion volume (CBF) and the respective set of TTP volumes were used to create subcompartments to calculate sensitivity and specificity values for each TTP threshold. The TTP threshold of 4 seconds reliably identified hypoperfused tissue (sensitivity, 0.827) and excluded normoperfused tissue (specificity, 0.768). Increasing the TTP threshold to 6 seconds impaired the ability to detect hypoperfusion (sensitivity, 0.765) but improved the rate of correctly identified normoperfused tissue (specificity, 0.875). From this small sample size, it can be concluded that a TTP delay between 4 and 6 seconds is useful to differentiate cerebral hypoperfusion <20 mL/100 g per minute.

### Assessment of Penumbra

In 10 patients (5 with acute ischemic attacks 5 hours after symptom onset and 5 presenting in the subacute state after ischemic attack due to vascular stenosis), PWI/DWI revealed a mismatch between the volumes of TTP prolonged beyond 4 seconds and the volume of increased DWI signal. In these patients, CBF and CMRO₂ were measured by PET, and the volumes of increased OEF (>150%) was calculated. A comparison of the volumes of increased TTP and of increased OEF (Figure 3) demonstrated a high variability between the volumes identified by these modalities: all 10 patients showed areas of TTP prolongation on PW images (median volume, 162 cm³; range, 8 to 450 cm³). However, in only 6 of 10 patients was an elevated OEF identified on PET images (median volume, 65 cm³; range, 12 to 240 cm³). The areas of OEF elevation were always located within the areas of TTP prolongation but were significantly smaller and covered only 8% to 58% (median, 33%) of the TTP area. These preliminary data demonstrate a high sensitivity but a low specificity of the chosen threshold to identify penumbral tissue as defined by PET: in 40% of the patients with TTP >4, no OEF elevation was found. In the remaining 60% with OEF elevation and TTP >4, only a third of the TTP volume corresponded to elevated OEF. These findings may explain the poor relation between increased OEF and TTP values in a correlation analysis based on volumes of interest. The results of our small patient sample indicate that TTP threshold >4 seconds does not sufficiently discriminate between normal and increased OEF in ischemic tissue.
Conclusion

These preliminary data on the comparison of PET and DWI/PWI for assessment of perfusion, identification of irreversible tissue damage, and distinction of penumbra (the final analysis of 1 part has been published, and the other parts are in preparation) indicate that imaging with these different modalities yields complementary information on the dynamics of pathophysiological events in ischemic brain tissue. The findings of DWI/ADC imaging correlate well with those of FMZ PET and predict the final infarct extension. However, the increased DWI signal carries a considerable false-positive rate, a clinically important restriction of DWI imaging correlate with clinical outcome. A mismatch volume in PWI/DWI does not reliably reflect misery perfusion as defined by PET. Despite the importance of MRI in clinical practice for the selection of patients who might benefit from revascularization procedures, the differences between the imaging methods and their specific methodological restrictions should be taken into account when results are compared and definitions of various tissue conditions are transferred between the modalities.

References

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