MRI Perfusion Maps in Acute Stroke Validated With 15O-Water Positron Emission Tomography

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Background and Purpose—Perfusion-weighted imaging maps are used to identify hypoperfusion in acute ischemic stroke. We evaluated maps of cerebral blood flow (CBF), cerebral blood volume, mean transit time, and time to peak (TTP) in acute stroke by comparison with positron emission tomography.

Methods—Perfusion-weighted imaging and positron emission tomography were performed in 26 patients with acute ischemic stroke (median 18.5 hours after stroke onset, 65 minutes between MRI and positron emission tomography). The perfusion-weighted imaging-derived maps of CBF, cerebral blood volume, mean transit time, and TTP delay were compared with quantitative positron emission tomography CBF. A receiver-operating characteristic curve analysis identified the best perfusion-weighted imaging map and threshold to identify hypoperfusion <20 mL/100 g/min, a widely used measure of penumbral flow.

Results—Individual regression analysis of positron emission tomography CBF and perfusion-weighted imaging values were strong for CBF and TTP delay and weaker for mean transit time and cerebral blood volume, but the pooled analysis showed a large variance. Receiver-operating characteristic curve analysis identified TTP and CBF maps as most predictive (median area under the curve = 0.94 and 0.93). Penumbral flow thresholds were <21.7 mL/100 g/min (CBF), <1.5 mL/100 g (cerebral blood volume), >5.3 seconds (mean transit time), and >4.2 seconds (TTP). TTP and CBF maps reached sensitivity/specificity values of 91%/82% and 89%/87%.

Conclusion—In our sample, maps of CBF, TTP, and mean transit time yielded a good estimate of penumbral flow. The performance of TTP maps was equivalent to deconvolution techniques using an arterial input function. For all maps, the application of a predefined threshold is mandatory and calibration studies will enhance their use in acute stroke therapy as well as in clinical stroke trials. (Stroke. 2010;41:443-449.)

Key Words: acute stroke ■ cerebral blood flow ■ cerebral ischemia ■ perfusion-weighted magnet resonance imaging ■ positron emission tomography ■ penumbra

Detecting and rescuing the ischemic penumbra is the main target of acute stroke therapy. In clinical studies, diffusion-weighted MRI and perfusion-weighted (PW) MRI help to estimate the tissue at risk and their adequate use is an ongoing challenge.

However, there are several concerns, how precise the penumbral flow threshold of functionally compromised but viable tissue (<20 mL/100 g/min as established by O15-water positron emission tomography [PET]) can be estimated by PW-based cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP) in acute human stroke and which of these maps should be preferred. One possible approach is the direct comparison of quantitative PW MRI maps with a reference method for quantitative perfusion imaging. So far, PW MRI maps were mainly validated with respect to infarct delineation on follow-up MRI. This technique is straightforward but suffers from the uncertainty of perfusion changes between early MRI and follow-up imaging. Few previous studies used comparative imaging with, for example, O15-water PET for in vivo perfusion measurement in the acute stroke setting, but a direct comparison of all 4 PW imaging parameters, including a detailed threshold based receiver-operating characteristic (ROC) curve analysis with respect to their ability to detect the penumbral threshold, is not yet available.

The focus of the present study is the performance of PW imaging to identify the penumbral flow threshold. We (1) performed a back-to-back comparison of quantitative PW MRI maps with quantitative 15O-water PET; (2) identified the best PW imaging map; and (3) the optimal threshold of each PW imaging map in terms of clinical application.

Materials and Methods

Patients

In a prospective imaging study, patients presenting with acute and subacute ischemic hemispheric stroke in our university hospital
between March 2003 and 2006 were included if MRI and subsequent quantitative PET imaging were feasible. Small vessel strokes and pure subcortical strokes were excluded. Patients undergoing thrombolysis or patients with a change of their National Institute of Health Stroke Scale score $>2$ points during the imaging procedure (measured at inclusion into the study, before MRI and before PET imaging) were excluded. The time delay between MRI and PET imaging was kept as short as possible. The imaging procedure was supervised by an experienced stroke neurologist under continuous monitoring according to stroke unit standards. Part of this patient population has been described in previous publications of our group.\(^7\)\(^9\)\(^10\) All patients gave informed consent and the study was approved by the local ethics committee.

**Magnetic Resonance Imaging**

MRI was performed on a 1.5-T whole-body scanner (Philips Intera Master). PW images were acquired in an axial direction (20 slices, 6-mm slice thickness, 0.6-mm interslice gap, field of view 23 cm) using multishot 3-dimensional T2*-weighted gradient echo echoplanar imaging sequences (PRESTO; effective TE 25 ms, flip angle 9°, echoplanar imaging factor 17, matrix 64×51, resulting voxel size 3.6×3.6×6.0 mm). The perfusion study consisted of 60 measurements at intervals of 1.3 seconds after a standardized intravenous injection of 20 mL gadolinium-DTPA (Magnevist; Schering AG) at a flow rate of 10 mL/s followed by rapid infusion of 20 mL saline with use of a power injector.

**Positron Emission Tomography**

PET was performed in a resting state on an ECAT EXACT HR Scanner (Siemens/CTI). CBF was acquired in a 2-dimensional data acquisition mode providing 47 contiguous 3-mm slices of 5-mm full-width half-maximum in plane-reconstructed resolution. After intravenous bolus injection of 15O-water (60 mCi=2.2 GBq), the tracer distribution was measured for 90 seconds. Continuous arterial blood sampling (radial artery) was used to calculate absolute CBF values (for details, see Raichle et al\(^11\)).

**Data Postprocessing**

The postprocessing of the PW raw images was performed by a specific software, STROKETOOL, Version 2.3 (DIS, Düsseldorf, Germany).\(^2\) PW raw images were processed on a pixel-by-pixel basis to generate maps of TTP from the tissue response curve as well as CBF, CBV, and MTT using the model-independent nonparametric basis to generate maps of TTP from the tissue response curve as well as CBF, CBV, and MTT using the model-independent nonparametric standard singular value decomposition deconvolution method described by Ostergaard.\(^11\)\(^14\)

The arterial input function was defined under visual control by 5 to 10 intravascular voxels within the proximal segment of the middle cerebral artery (MCA) and the distal segment of the internal carotid artery of the unaffected hemisphere. The resulting input function was visually inspected for peak sharpness, amplitude width, and bolus peak time to select only nondistorted bolus curves.\(^15\)

**Image Analysis**

Image analysis was performed by investigators blinded to clinical and other imaging data. MRI and PET image analysis was performed using an Interactive Data Language (IDL)-based multimodal imaging tool (VINCI). Due to the different spatial resolution in the z-axis, PET images were resliced to the MRI images and then realigned by an automated observer-independent algorithm.\(^16\)

For every patient, a 3-dimensional brain mask, created by the individual T1 image, was used to exclude the ventricles, most of the periventricular white matter, and large vessels and the sinuses. Ventricles and periventricular white matter were excluded by manual segmentation on each slice. Within this individual atlas, the region of interest (ROI) analysis of the MRI and PET images was performed. Using VINCI, we placed 10-mm circular ROIs on the axial cuts of the 3-dimensional brain mask along the cortex in both the affected and unaffected hemisphere. All ROIs were then copied on to the coregistered PW maps as well as on the PET CBF maps. The mean ROI values were used for further analysis. Voxels within the infarcted tissue without contrast bolus were excluded from further analysis\(^17\) (Figure 1).

**Data Analysis**

**Regression and Bland-Altman Analysis**

The mean ROI values for PET CBF, CBV, MTT, and TTP maps were plotted against their corresponding PET CBF values for each patient separately as well as for all patients together. A linear regression analysis was performed. A Bland-Altman plot for PW CBF and PET CBF was calculated to illustrate the method-specific differences.

**ROC Curve Analysis**

The accuracy of PW MRI to detect hypoperfusion was determined by ROC curve analysis. We used PET to define penumbral flow by CBF values $<20$ mL/100 g/min.

In a first step, the ROC curve analysis was done for every patient and each modality separately. In a second step, the PW map with the greatest area under the ROC curve (AUC) was identified. The AUC represents the probability that a PW image will be correctly classified as normal or abnormal as defined by PET CBF $<20$ mL/100 g/min. In a third step, the best threshold for each PW parameter was then defined separately for each patient as the equal sensitivity and specificity threshold. The median and interquartile range (IQR) of these thresholds as well as their sensitivity and specificity were calculated and compared across all patients.

**Statistics**

Because most of the study values were not normally distributed, the results were presented as median and IQR if not indicated otherwise. The regression analysis was performed to measure the strength of the relation. A Bland-Altman analysis was used for PET CBF and PW CBF values. We tested for differences in AUC values among CBF, CBV, MTT, and TTP for all measures using the Mann-Whitney rank sum test. Statistical significance was set at $P<0.05$. Data were analyzed by Sigmasat 3.11 (SYSTAT Software, Inc) and Med Calc Software (Version 11).

**Results**

**Clinical Data**

Of the 26 patients (median age, 56.5 years), 17 patients were imaged within 24 hours after stroke (median, 9.2 hours) and 9 were measured beyond 24 hours (median, 48 hours). The median time delay between MRI and PET was 65 minutes (Table 1).
Part A: Regression and Bland-Altman Analysis

On visual inspection, an excellent spatial correspondence of the hypoperfused areas (as defined by PET) was found on PW maps of CBF, CBV, TTP, and MTT (Figure 1).

The mean ROI values for PW CBF, CBV, MTT, and TTP maps were plotted against their corresponding PET CBF values for each patient as well as for all patients together. The linear regression analysis showed a good intraindividual dependency, but $R^2$ values showed a substantial variability (CBF $R^2 = 0.67$ [IQR: 0.47 to 0.75], CBV $R^2 = 0.33$ [IQR: 0.17 to 0.43], MTT $R^2 = 0.45$ [IQR: 0.33 to 0.63], TTP delay $R^2 = 0.59$ [IQR: 0.49 to 0.66]). In contrast, the regression analysis of the pooled data was weak and did not show a linear characteristic (Figure 2).

The Bland-Altman plot of all 2975 ROIs (affected and unaffected hemisphere) showed a mean difference of $-8$ mL/100 g/min between absolute PET CBF and MRI CBF values. This analysis yielded a slight overestimation of hypoperfusion by MRI CBF and an increase of variability with increasing flow values (Figure 3).

Part B: ROC Analysis

The ROC curve analysis was performed separately for every patient’s ROIs and each modality. Representative data of one patient are displayed in Figure 4. The mean values of all patients (ie, the pooled analysis) are summarized in Table 2. The highest mean AUC values (indicating the best detection of penumbral flow) were found for CBF (0.93) and TTP (0.94). MTT (0.86) and CBV (0.79) showed significantly lower AUC values ($P<0.05$). The optimal thresholds (median values of the pooled analysis) identified by the equal sensitivity and specificity threshold method are shown in Table 2.

### Table 1. Clinical Data, Vessel Pathology, and Volumetric Data of All Patients With Comparative Imaging*

<table>
<thead>
<tr>
<th>ID</th>
<th>Site</th>
<th>Age, Years</th>
<th>NIHSS</th>
<th>Stroke to Imaging, Hours</th>
<th>MRI to PET, Minutes</th>
<th>ICA Stenosis IPSI, %</th>
<th>ICA Stenosis CONTR, %</th>
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*Stroke to imaging, time delay between stroke onset and MRI scan; MRI to PET, time between the scans. The degree of stenosis of the ICA was classified in percent by ultrasound.

NIHSS indicates National Institutes of Health Stroke Scale; ICA, internal carotid artery; IPSI, ipsilateral to the site of ischemia; CONTR, contralateral; L, left; R, right; PCA, posterior cerebral artery.
Discussion

It was the aim of the present study to determine the accuracy of PW-derived maps in acute and subacute stroke. We have shown that (1) quantitative CBF as well as nondeconvolved TTP delay maps performed best in detecting the penumbral threshold; and that (2) for these maps, a CBF threshold <21.7 mL/100 g/min and a TTP delay threshold >4.2 seconds could identify the penumbral flow threshold with a sensitivity of 89% and 91% and a specificity of 87% and 82%, respectively. Although the median values provided promising results, the interindividual variance was considerable.

Based on the threshold independent AUC analysis, our results showed that the best performance to identify penumbral flow was comparable for the nondeconvolved maps of TTP compared with absolute CBF and MTT derived from standard singular value decomposition deconvolution. This is an interesting finding because TTP does not rely on deconvolution algorithms with input function. Nondeconvolved TTP maps are influenced by factors such as tracer arrival delay, tissue transit time, and arterial dispersion. Deconvolved measures on the other hand decouple tissue transit time from the previously mentioned arterial dispersion and tracer arrival delay. Therefore, if dispersion and tracer arrival contain relevant information for the detection of hypoperfusion, deconvolution might result in a reduced performance of PW imaging (for a detailed discussion, see Christensen et al4). Previous studies using MRI as a reference method

Figure 2. Scatterplots of the pooled ROI values comparing PET CBF and PW imaging CBF, CBV, MTT, and TTP delay. A linear regression analysis was performed across all patients as well as for every patient separately (see median R²).

Figure 3. The Bland-Altman plot for mean ROI values of PET-based and PW-based CBF across the whole brain.
investigated the performance of PW imaging parameters to predict infarct growth. They found that the diagnostic performance of MTT was significantly lower than that of CBF and the most predictive maps to be the nondeconvolved first moment and TTP maps. Both studies are broadly consistent with our results.

Based on the ROC analysis, we found a CBF threshold of <21.7 mL/100 g/min as the best estimate of penumbral flow (sensitivity 89%, specificity 87%). In a previous study using a volumetric approach in a smaller sample, we found a similar threshold of <20 mL/100 g/min (sensitivity 76%, specificity 96%). The consistency between the 2 methods further strengthens the validity of our data and emphasizes the usefulness of PW imaging CBF as a predictor of penumbral flow. There is only one study of 11 patients comparing relative PW imaging CBF with single photon emission CT CBF in an acute stroke setting. The best cutoff value to discriminate between the area of infarct growth and viable ischemic tissue was 48% of the unaffected hemisphere. This threshold was converted into <24 mL/100 g/min in normal human brain in mixed gray and white matter.

The most accurate CBV estimate of penumbral flow is <1.5 mL/100 g with a sensitivity of 82% and a specificity of 79%. There are no comparisons of PET with PW CBV in the literature in the acute stroke setting to establish a threshold and its validity for the detection of penumbral flow. The mentioned single photon emission CT CBV study of Liu et al found a relative CBV threshold for penumbra to be 87% of the unaffected hemisphere. This would result in a threshold of 1.95 mL/100 g if applied to our study. In a comparative single photon emission CT CBF study, Hatazawa et al found a threshold of relative PW CBF for penumbral flow of 85% resulting in a threshold of 1.9 mL/100 g in our group.

A TTP threshold of >4.2 seconds reaching a sensitivity of 91% and a specificity of 82% was the most accurate to detect the penumbral threshold. TTP was the only PW parameter map in our study without a deconvolution procedure. Four previous studies compared PET and PW imaging to validate TTP in acute and chronic stroke. Kajimoto et al compared 9 patients with chronic stroke in chronic occlusive carotid disease and found a TTP delay of >4 seconds (79% sensitivity, 96% specificity) to correspond to an increase of oxygen extraction fraction >0.52. Sobesky et al compared 11 patients with acute stroke using PET CBF in a volumetric seed-growing approach. An optimal TTP delay threshold of >4 seconds was found to have a sensitivity of 84% and a specificity of 77% to detect penumbral flow. In a second study, Sobesky et al found in 13 patients of acute and subacute stroke a TTP delay >6 seconds to best predict the penumbra volume (defined by oxygen extraction fraction >150%). The different approach might have accounted for the difference from the present study. A more recent small study of 5 patients with acute stroke found a TTP delay threshold of >4.8 seconds to best predict penumbra, which is close to our findings. Using MRI only, Neumann-Haefelin et al reported that a TTP delay >6 seconds best predicted diffusion-weighted imaging growth, whereas a TTP delay >4 seconds correlated best with acute-stage neurological deficit.23 Our findings are again consistent with these reports and further strengthens the TTP delay threshold to lie between >4 and 5 seconds.

The most accurate MTT penumbral threshold is >5.3 seconds with a sensitivity of 88% and a specificity of 78%. One previous comparative PET versus PW MTT study without ROC analysis found a threshold of >6 to 7 seconds. A study comparing Xenon CT with PW MTT revealed a MTT threshold as high as >10 seconds. This value was derived from a ROC curve analysis, but the patients were scanned 12 days (median) after symptom onset. Thus, no significant amount of ischemic penumbra was likely to be present and higher values are expected.

There are several methodical issues that have to be considered when interpreting our results. First, accurate calculation of PW imaging maps might not be possible in areas of severe ischemia in which contrast flow is extremely de-

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**Table 2. Median Equal Sensitivity and Specificity Threshold (See Text) Penumbra Cutoff Values of CBF, CBV, MTT, and TTP Delay With Its Corresponding Mean Sensitivity and Specificity and the Median AUC Results Derived From the ROC Curve Analysis**

<table>
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<tr>
<th>Penumbral Flow Threshold</th>
<th>CBV, mL/100 g/min</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
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<tr>
<td>CBF, mL/100 g/min</td>
<td>21.7 (19.9–32)</td>
<td>0.89 (0.82–0.96)</td>
<td>0.87 (0.81–0.92)</td>
<td>0.92 (0.88–0.98)</td>
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<tr>
<td>CBV, mL/100 g</td>
<td>1.5 (0.9–1.8)</td>
<td>0.82 (0.75–0.88)</td>
<td>0.79 (0.64–0.91)</td>
<td>0.79 (0.71–0.93)</td>
</tr>
<tr>
<td>MTT, seconds</td>
<td>5.3 (3.9–6.9)</td>
<td>0.88 (0.82–0.96)</td>
<td>0.78 (0.72–0.86)</td>
<td>0.86 (0.82–0.92)</td>
</tr>
<tr>
<td>TTP delay, seconds</td>
<td>4.2 (2.8–5.8)</td>
<td>0.91 (0.87–0.96)</td>
<td>0.82 (0.81–0.91)</td>
<td>0.94 (0.89–0.97)</td>
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</table>

*Variation is given as IQR.
Our software assigns zero values to these voxels and we prudently excluded all these “artificial” ischemic core voxels from further analysis. Other algorithms assign these voxels predefined maximum values that are difficult to distinguish from “real” hypoperfusion, which might account for higher MTT threshold values in some studies. Second, there are differences between the standard singular value decomposition deconvolution method and other deconvolution methods such as circular singular value decomposition deconvolution and Fourier transformation. Third, a direct comparison between PW imaging and flow measurement with PET, single photon emission CT, or Xenon CT was performed in only a few studies of acute ischemic stroke. Most studies compared early PW imaging and diffusion-weighted imaging measures with stroke evolution in late MRI images. This method implies the disadvantage of flow changes in between the scans that might confound the results. Fourth, our approach of a ROC curve analysis was used by only a few studies. It seems adequate because it allows the identification of the optimal threshold in terms of sensitivity and specificity. The use of small ROIs might be superior to a voxel-based approach because PW imaging–echoplanar images suffer from distortion and make coregistration on a voxel level difficult. Fifth, in our study, the best cutoff threshold for penumbral flow using the ROC curve analysis was determined by the equal sensitivity and specificity threshold. Depending on the individual clinical setting, a higher sensitivity or specificity might be required and therefore the optimal threshold values might be different.

Sixth, the predefined penumbral flow threshold for CBF is valid for gray matter only and the inclusion of white matter may lead to lower thresholds. We minimized this error by placing the ROIs along the cortex and created a brain mask that excluded most of the periventricular white matter voxels. Therefore, the results are not applicable to pure subcortical infarcts. Seventh, perfusion changes during the back-to-back imaging procedure between PET and PW imaging cannot be ruled out with certainty, but we minimized this effect because we kept time between imaging modalities as short as possible (median time between MRI and PET 65 minutes, 17 of 26 patients within 90 minutes) and only included patients with stable clinical presentation during the imaging procedure. Eighth, the arterial input function technique is sensitive to postprocessing errors and a standardized protocol to choose the arterial input function has not yet been validated. Ninth, a standardized imaging protocol including PW imaging sequence and postprocessing methods should be used to make results of different centers more comparable. For a detailed discussion of these issues, see Zaro-Weber et al.

In summary, our study yields encouraging results for the use of MRI-based flow thresholds in acute stroke. The easy to obtain nondeconvolved parameter PW TTP delay performed at least as well as or even better than the deconvolution-based methods PW CBF and PW MTT for the detection of penumbral flow. The interindividual variability, as previously described, needs further specification and the development of MR-based correction factors will enhance the use of PW imaging in the clinical setting as well as in clinical stroke studies.

Acknowledgments
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Disclosures
None.

References


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