Which Time-to-Peak Threshold Best Identifies Penumbral Flow?

A Comparison of Perfusion-Weighted Magnetic Resonance Imaging and Positron Emission Tomography in Acute Ischemic Stroke

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Background and Purpose—In acute ischemic stroke, the hypoperfused but viable tissue is the main therapeutic target. In clinical routine, time-to-peak (TTP) maps are frequently used to estimate the hemodynamic compromise and to calculate the mismatch volume. We evaluated the accuracy of TTP maps to identify penumbral flow by comparison with positron emission tomography (PET).

Methods—Magnetic resonance imaging (MRI) and PET were performed in 11 patients with acute ischemic stroke (median 8 hours after stroke onset, 60 minutes between MRI and PET imaging). The volumes defined by increasing TTP thresholds (relative TTP delay of $2, 4, 6, 8$, and $>10$ seconds) were compared with the volume of hypoperfusion ($<20$ mL/100 g per min) assessed by $^{15}$O-water PET. In a volumetric analysis, each threshold’s sensitivity, specificity, and predictive values were calculated.

Results—The median hypoperfusion volume was 34.5 cm$^3$. Low TTP thresholds included large parts of the hypoperfused but also large parts of normoperfused tissue (median sensitivity/specificity: 93%/60% for TTP $2$) and vice versa (50%/91% for TTP $>10$). TTP $4$ seconds best identifies hypoperfusion (84%/77%). The positive predictive values increased with the size of hypoperfusion.

Conclusion—This first comparison of quantitative PET-CBF with TTP maps in acute ischemic human stroke indicates that the TTP threshold is crucial to reliably identify the tissue at risk; TTP $4$ seconds best identifies penumbral flow; and TTP maps overestimate the extent of true hemodynamic compromise depending on the size of ischemia. Only if methodological restrictions are kept in mind, relative TTP maps are suitable to estimate the mismatch volume. (Stroke. 2004;35:-.)

Key Words: cerebral blood flow ■ magnet resonance imaging ■ perfusion ■ stroke, acute ■ tomography, emission computed
continuous monitoring and surveillance of an experienced stroke neurologist. The study was approved by the local ethics committee.

MRI was performed on a 1.5-T whole-body scanner (Philips Intera Master; Best). PW images were assessed in 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 EPI sequences (PRESTO; TR 17 ms, effective TE 25 ms, flip angle 9°, EPI factor 17, matrix 64×51, resulting voxel size 3.6×3.6×6 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) with a flow rate of 10 mL/s.

PET was performed in a resting state on an ECAT EXACT HR Scanner (Siemens/CTI). CBF was assessed 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 was used to calculate absolute CBF values.\(^8\)

Data Postprocessing

The TTP maps were calculated by a custom-made IDL-based software (IDL 6.0; Interactive Data Language, Research System Inc.). The TTP was defined as the time point of maximum intensity loss after the passage of the contrast agent. Ischemic areas are characterized by a delay of tracer arrival and a TTP increase. For data poling, the mean value of a region of interest covering the contralateral middle cerebral artery (MCA) territory in a slice including the basal ganglia was subtracted from the absolute TTP values.\(^8\)

PET-CBF images were coregistered to the original TTP images by an automatic matching routine under visual control. This routine uses the intensity histograms of the brain volumes and searches for the transformation with the highest mutual information.\(^12\) After coregistration, CBF and TTP images were resliced to a similar voxel size (3.6×3.6×6.6 mm).

Within an individual brain atlas of white and gray matter (Figure 1a), the volume of hypoperfusion <20 mL/100 g per min (red) and the volumes of different TTP delays (blue) were generated by thresholding the respective images (b). In a volumetric comparison, the subcompartments were labeled for each TTP threshold (c): correctly identified hypoperfusion (yellow, CBF <20 and TTP >x), hypoperfused tissue not identified by the TTP threshold (red, CBF <20 and TTP <x), normoperfused tissue falsely identified as pathological on TTP maps (blue, CBF >20 and TTP >x), and normoperfused tissue correctly identified as normal on TTP maps (gray, CBF >20 and TTP <x).

### TABLE 1. Individual Patient Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Onset of Symptom to PWI (h)</th>
<th>PWI to PET (min)</th>
<th>Volume of Hypoperfusion (cm³)</th>
<th>NIHSS Score</th>
<th>Side of Ischemia</th>
<th>Vessel Pathology/Degree of Stenosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37/F</td>
<td>16</td>
<td>130</td>
<td></td>
<td>198.0</td>
<td>17</td>
<td>RMCA, ACA</td>
<td>LMCA/100</td>
</tr>
<tr>
<td>2</td>
<td>57/M</td>
<td>2</td>
<td>45</td>
<td>140</td>
<td>34.5</td>
<td>11</td>
<td>LMCA</td>
<td>LMCA/100</td>
</tr>
<tr>
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<td>140</td>
<td>1.2</td>
<td>1</td>
<td>RMCA</td>
<td>RICA/100</td>
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<tr>
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<td>60</td>
<td></td>
<td>362</td>
<td>13</td>
<td>RMCA, ACA</td>
<td>RICA/100</td>
</tr>
<tr>
<td>5</td>
<td>56/M</td>
<td>5</td>
<td>140</td>
<td></td>
<td>113.6</td>
<td>6</td>
<td>LMCA</td>
<td>LICA/100</td>
</tr>
<tr>
<td>6</td>
<td>62/M</td>
<td>4.5</td>
<td>60</td>
<td></td>
<td>5.0</td>
<td>5</td>
<td>LMCA</td>
<td>RICA/100</td>
</tr>
<tr>
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<td>60</td>
<td></td>
<td>210.2</td>
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<td>LMCA, ACA</td>
<td>LICA/100</td>
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<tr>
<td>8</td>
<td>74/F</td>
<td>4</td>
<td>100</td>
<td></td>
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<td>10</td>
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<td>LICA/70</td>
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<tr>
<td>9</td>
<td>55/M</td>
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<td></td>
<td>5.3</td>
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<td>—</td>
</tr>
<tr>
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<td>46/M</td>
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<td></td>
<td>266.0</td>
<td>22</td>
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<td>LMCA</td>
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<tr>
<td>Median</td>
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<td>60</td>
<td></td>
<td>34.5</td>
<td>10</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Min</td>
<td>37</td>
<td>1.8</td>
<td>20</td>
<td></td>
<td>1.2</td>
<td>1</td>
<td>—</td>
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<tr>
<td>Max</td>
<td>78</td>
<td>20</td>
<td>140</td>
<td></td>
<td>362.0</td>
<td>22</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

L indicates left; R, right; MCA, middle cerebral artery; ACA, anterior cerebral artery; ICA, internal carotid artery; M, male; F, female; NIHSS, National Institutes of Health Stroke Scale; Min, minimum; Max, maximum.
Statistics

A nonparametric approach was used for statistical analysis because the data were not normally distributed (Kolmogorov–Smirnov test). If not otherwise indicated, data are given as median and range. The correlation analysis was performed by Spearman rank correlation with correction for multiple comparisons. The group differences were tested by an ANOVA on ranks procedure (Student-Newman-Keuls). All statistic analysis was performed with Sigmastat 3.00 (SPSS Inc, 2003).

Results

For clinical data, see Table 1. The pooled analysis of all 11 patients indicated that TTP >2 included large parts of the affected hemisphere and led to a clear overestimation of CBF <20. Therefore, this threshold showed a poor specificity (median 60%) but a high sensitivity (93%) (Figure 2 and Table 2). Increasing the threshold to higher TTP values reduced the TTP volume and approximated it to CBF <20 mL/100 g per minute as assessed by 15O-water PET. The threshold for the detection of hypoperfusion (<20 mL/100 g per minute) was therefore strongly associated with CBF values <20 mL/100 g per minute. In contrast, the median positive predictive value was poor (median 32% for TTP >2, continuously increasing to 59% for TTP >10). However, the large interindividual range (1% to 98% for TTP >2, 6% to 92% for TTP >10) indicated a marked difference among the patients and was explained by a significant correlation with the size of hypoperfusion (for all negative predictive values: r = −0.95 to −0.98 and P < 0.005; for the positive predictive values: r = 0.95, P < 0.005 for TTP >2, gradually decreasing to r = 0.74, P < 0.05 for TTP >10). Hence, the percentage of truly hypoperfused tissue among the voxels with a TTP value above a chosen threshold increased with increasing hypoperfusion size (which is in line with the dependency of predictive values on the prevalence described by the Bayes theorem). Three examples of comparative imaging with different patterns of congruence in CBF and TTP imaging are illustrated in Figure 3.

Conclusions

It was the aim of the present study to determine the accuracy of TTP maps in acute ischemic stroke. Different TTP thresholds were tested for their ability to identify hypoperfusion <20 mL/100 g per minute as assessed by 15O-water PET. The best estimate was found for a TTP delay of >4 seconds relative to the contralateral hemisphere and could correctly identify 84% of the hypoperfused and 77% of the normoperfused tissue. This first comparison of TTP with PET-CBF in the setting of acute ischemic human stroke indicates that this simple PWI parameter is a useful estimate of ischemic

### Table 2. Sensitivity, Specificity, and Predictive Values of the Different TTP Thresholds for the Identification of Hypoperfusion <20 mL/100 g per Minute

<table>
<thead>
<tr>
<th>TTP &gt;2</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>93 (83–95)</td>
<td>60 (42–77)</td>
<td>32 (13–64)</td>
<td>98 (87–99)</td>
<td></td>
</tr>
<tr>
<td>TTP &gt;4</td>
<td>84 (64–91)</td>
<td>77 (60–89)</td>
<td>43 (16–73)</td>
<td>96 (85–99)</td>
</tr>
<tr>
<td>TTP &gt;6</td>
<td>77 (45–86)</td>
<td>86 (70–94)</td>
<td>55 (16–77)</td>
<td>94 (82–99)</td>
</tr>
<tr>
<td>TTP &gt;8</td>
<td>67 (45–77)</td>
<td>88 (76–97)</td>
<td>59 (26–83)</td>
<td>93 (79–99)</td>
</tr>
<tr>
<td>TTP &gt;10</td>
<td>50 (26–67)</td>
<td>91 (78–98)</td>
<td>59 (30–82)</td>
<td>93 (78–99)</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value.

Data are given as median values and 25th and 75th percentiles of the individual results from 11 patients.
compromise but has important methodical limitations that have to be considered in the routine use of stroke MRI. Relative TTP maps are only indirect surrogates of CBF and do not represent the best performance of MRI-derived perfusion imaging. However, they are used in clinical routine because they clearly delineate hemodynamic alterations, yield satisfactory results compared with quantitative methods, and do not rely on deconvoluting algorithms, calibration with PET data, or the choice of adequate input functions.

Since the introduction of stroke MRI, comparative studies with single-photon emission computed tomography (SPECT) and PET intended to validate PWI maps. Comparative studies with PET have not yet been performed in acute stroke but only in healthy volunteers and in patients with chronic occlusive disease with several days between PET and MRI. 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 regions of interest. Accordingly, an association of the TTP delay and decreased perfusion was recently described in chronic stroke patients.

These results, however, are difficult to translate into the clinical setting. A region-based analysis does not necessarily represent the whole brain volume and distinct thresholds are necessary to use PW/DW-MRI as a tool for decision-making in acute stroke trials. We therefore used stepwise increasing TTP thresholds and estimated their “match” to hypoperfusion. The CBF value of <20 mL/100 g per minute was chosen as the target volume because it defines the widely accepted upper flow limit for penumbral flow that still enables tissue integrity but causes a clinical deficit and is at high risk to turn into infarction. The correct identification of this flow threshold by TTP, combined with the extent of highly probable tissue loss indicated by DWI, would therefore best defines the volume of mismatch based on TTP and DWI maps. The inverse relation of sensitivity and specificity with increasing TTP thresholds as found in our study emphasizes that a simple visual assessment of TTP alterations is not suitable for the definition of the tissue at risk. A TTP threshold of >2 seconds, approximately corresponding to the visual impression of “hemodynamic compromise,” includes 93% (median) of the hypoperfused tissue but discriminates only 60% of the normoperfused tissue as normal. In contrast, a TTP threshold of >10 seconds only identifies 50% of the hypoperfused tissue but labels 91% of the normoperfused tissue as normal. The lack of a complete “match” between the imaging modalities is partly explained by the method specific properties. TTP maps only yield an estimation of CBF as they indicate the time point of maximal signal intensity loss during the passage of a strictly intravascular tracer within several seconds. However, PET with 15O-water quantitatively assesses CBF as the concentration of a partly diffusible tracer integrated over a scanning time of several minutes. This fundamental difference (time point versus time integral) leads to an increased method intrinsic susceptibility of TTP maps (eg, to movement artifacts, collateral flow, or individual hemodynamic properties).

In our study, the best estimate of penumbral flow was found for a TTP delay of >4 seconds (sensitivity 84%, specificity 77%). This threshold places the emphasis on a high sensitivity (ie, on the identification of hypoperfused tissue), but it can be modified according to the underlying clinical question and the respective characteristics can be derived from our serial analysis. Our findings provide the pathophysiologial correlate of the TTP thresholds derived from acute MRI studies. Here, the volume of a TTP delay between >5 and >8 seconds was strongly associated to infarct growth, whereas the volume of a TTP delay of >4 seconds correlated to the clinical deficit. Considering that the difference of the study designs obviate a direct comparison, our serial analysis explains these results by the amount of included penumbral flow that decreases with higher TTP thresholds.

The interindividual variation of our comparative data were large and indicated that the applicability of the TTP method differs among the patients. As for the sensitivity and specificity values, a dependency on the type of vessel occlusion might be speculated but cannot be derived from our patient sample. More important for clinical application, and in line with previous findings, the median positive predictive value (ie, the percentage of truly hypoperfused tissue among the tissue with elevated TTP values) was low, but showed a huge individual range and was inversely correlated to the hypoperfusion volume. This finding indicates that even the optimal TTP threshold in terms of sensitivity and specificity may overestimate the hypoperfusion volume and that this overestimation was more pronounced in cases of small ischemia.

**Figure 3.** PET-CBF (left), TTP map (middle), and the resulting atlas for TTP >4 seconds with the respective subcompartments (right) in 3 different patients (for atlas colors see Figure 1). (a) In the case of a large MCA ischemia, a good agreement was found between PET and TTP. (b) In the example of a middle-sized ischemia, the best match for the identification of hypoperfusion (yellow) still left normoperfused tissue labeled as pathologic on TTP (blue). (c) In the case of a small cortical ischemia, the volume of TTP >4 largely overestimated CBF <20.
Several methodical issues concerning the comparative imaging approach have to be addressed. According to previous studies and to the routine use of TTP maps, we did not distinguish between gray and white matter. Because these compartments are better contrasted on CBF images than on TTP maps, the combined analysis may impair the sensitivity of TTP thresholds. We focused on early cerebral ischemia because the results obtained in healthy volunteers and patients with chronic occlusive diseases are not necessarily applicable in acute stroke. The time delay between the imaging modalities was therefore inevitable but was small in our study (median 60 minutes) and no changes in clinical presentation were observed. The distortion of PWI maps caused by fast scanning by echoplanar imaging sequences may cause spatial incongruencies in the assessment of small volumes, especially in the frontal and basal parts of the brain.

Because the analyzed volumes were sufficiently large or located in the deep MCA territory, this does not seem to hamper the essential of our findings.

In conclusion, the direct comparison of TTP maps and PET CBF in acute ischemic stroke leads to the following results: (1) a simple visual analysis of PWI data seems inappropriate and the applied TTP threshold is crucial to reliably identify the tissue at risk; (2) a relative TTP delay of >4 seconds best identifies the volume of penumbral flow and should therefore be used for the definition of the mismatch volume; and (3) even the TTP threshold with the best performance in terms of sensitivity and specificity includes a large portion of tissue with only modest hemodynamic compromise. Particularly in small ischemia, the TTP maps tend to overestimate the true extent of the “tissue at risk.” These limitations have to be considered in the routine use of TTP maps. A further analysis in a larger patient sample would allow us to define the value of TTP imaging with respect to the size of ischemia and the underlying vessel pathology. This specification is of major clinical interest to improve the selection of patients amenable to acute stroke therapy.

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References
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