Maps of Time to Maximum and Time to Peak for Mismatch Definition in Clinical Stroke Studies Validated With Positron Emission Tomography

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Background and Purpose—Perfusion-weighted imaging-derived maps of time-to-maximum (Tmax) are increasingly used to identify the tissue at risk in clinical stroke studies (eg, DEFUSE and EPITHET). Using quantitative positron emission tomography (PET), we evaluated Tmax to define the penumbral flow threshold in stroke patients and compared its performance to nondeconvolved time-to-peak (TTP) maps.

Methods—Comparative perfusion-weighted imaging and quantitative 15O-water PET images of acute stroke patients were analyzed using cortical regions of interest. A receiver-operating characteristic curve analysis described the threshold independent performance of Tmax (area under the curve) and identified the best threshold (equal sensitivity and specificity threshold) to identify penumbral flow (<20 mL/100 g/min on PET cerebral blood flow). The results were compared with nondeconvolved TTP and other current perfusion-weighted imaging maps using the Mann–Whitney rank-sum test.

Results—In 26 patients (time delay between MRI and PET, 65 minutes), the best threshold for penumbral flow was 5.5 seconds for Tmax (median; interquartile range, 3.9–6.6; sensitivity/specificity, 88%/89%). The area under the curve value was 0.95 (median; interquartile range, 0.93–0.97). Deconvolved Tmax did not perform significantly better than TTP (P=0.34).

Conclusion—Maps of Tmax detected penumbral flow but did not perform better than the easy-to-obtain maps of nondeconvolved TTP. Thus, “simple” TTP maps still remain suitable for clinical stroke studies if detailed postprocessing is not feasible. (Stroke. 2010;41:2817-2821.)

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

The main target of acute stroke therapy is detecting and rescuing the ischemic penumbra. In acute stroke MRI, the mismatch between hypoperfused tissue assessed by perfusion-weighted imaging (PWI) and the ischemic core represented by the diffusion-weighted imaging lesion approximates the ischemic penumbra.1,2 The benefit of reperfusion in mismatch tissue has been addressed in recent clinical trials (eg, DIAS, DIAS II, DEDAS, DEFUSE, EPITHET). Importantly, the definition of mismatch in stroke trials, as in the DEFUSE and EPITHET, as well as in the current DEFUSE-2 and EXTEND trials, is based on a penumbra flow (PF) threshold defined by maps of time to maximum (Tmax).3,4

Thus, it is of considerable interest how precise the PF threshold (commonly defined by cerebral blood flow (CBF; <20 mL/100 g/min) can be estimated by maps of Tmax. Additionally, it should be clarified how Tmax relates to nondeconvolved time-to-peak (TTP) and other PWI maps. So far, Tmax was mainly compared with 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.5–9 The direct comparison of maps of Tmax with a reference method for perfusion imaging,7,10 eg, O15-water PET in the acute stroke setting, is desirable.

In this study, we evaluated the performance of Tmax using a threshold-independent receiver-operating characteristic (ROC) curve analysis approach. We assess the optimal Tmax PF threshold, evaluate the performance of Tmax, and compare it to “simple” nondeconvolved TTP with respect to the detection of PF.

Materials and Methods

Patients
The presented data contain a subset of a prospective imaging study of patients with acute and subacute ischemic hemispheric stroke.
Patients were included if MRI and subsequent quantitative PET imaging were feasible. Small vessel strokes and pure subcortical strokes were excluded. Part of this patient population and the inclusion criteria have been described in previous publication by our group. All patients gave informed consent and the study was approved by the local ethics committee.

**MRI and PET**
Data acquisition and postprocessing have been described in detail in a recent study. In brief, MR imaging was performed on a 1.5-T whole-body scanner (Philips Intera Master; Best). PW images were acquired using gradient-echo EPI sequences (repetition time, 1.3 seconds; effective echo time, 25 ms; 20 slices; slice thickness, 6 mm; interslice gap, 0.6 mm; field of view, 23 cm). PET was performed in a resting state on an ECAT EXACT HR Scanner (Siemens/CTI). CBF was acquired in a 2-dimensional 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.

**Data Postprocessing**
The postprocessing of the PW raw images was performed by STROKE TOOL, version 2.3 (DIS) on a pixel-by-pixel basis to generate maps of Tmax from the tissue-response curve using the nonparametric standard singular value decomposition deconvolution method. Tmax represents the time delay to the maximum of the nonparametric standard singular value decomposition deconvolution method. Tmax represents the time delay to the maximum of the nonparametric standard singular value decomposition deconvolution method.

**Image Analysis**
Image analysis was performed using a multimodal imaging tool (VINCI, Max Planck Institute for Neurological Research, Cologne, Germany). PET images were resized to the MRI images and then realigned by an automated observer-independent algorithm. 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, 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 ROI on the axial cuts of the 3-dimensional brain mask along the cortex in the affected and unaffected hemisphere. All ROI were then copied onto the coregistered PET-CBF map and on the maps of Tmax. The mean ROI values were used for further analysis. Voxels within the infarcted tissue without contrast bolus arrival were excluded from further analysis (Figure 1).

**Regression Analysis**
The mean ROI values for Tmax 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.

**ROC Curve Analysis**
The accuracy of Tmax to detect hypoperfusion was determined by a ROC curve analysis. We used PET to define PF by CBF values <20 mL/100 g/min. In a first step, the ROC curve analysis was performed for every patient separately. In a second step, the area under the ROC curve (AUC) for Tmax was identified. The AUC represents the probability that a ROI will be correctly classified as normal or abnormal as defined by PET-CBF <20 mL/100 g/min. The AUC is an important indicator of the PWI performance to detect the penumbral threshold independently from the selected cut-off value. The closer the AUC is to 1, the better is the performance of the PWI map. In a third step, the best threshold for Tmax was defined separately for each patient as the equal sensitivity and specificity threshold. The median and interquartile range (IQR) of these individual thresholds as well as their sensitivity and specificity values were calculated in a pooled analysis.

**Comparison to TTP and Other PWI Modalities**
We compared the performance of Tmax with TTP and other PW modalities (mean transit time [MTT], CBF, and CBV). They were analyzed in the same way as Tmax. A detailed description of these parameters and their analysis were presented previously. In summary, 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 standard singular value decomposition deconvolution method described by Ostergaard. Image acquisition and all further image postprocessing and analysis, including placement of identical ROI, were performed in line with Tmax.

**Figure 1.** Region of interest analysis of positron emission tomography (PET) cerebral blood flow and perfusion-weighted Tmax. Circular regions of interest (10 mm) were manually drawn along the cortical rim and copied on the PET and perfusion-weighted imaging maps. Ventricles and periventricular white matter, large arteries, sinus, and areas of severely delayed contrast agent were excluded.

**Figure 2.** Scatter plot of the pooled region of interest values comparing positron emission tomography cerebral blood flow and perfusion-weighted Tmax. A linear regression analysis was performed across all patients ($R^2$) and for every patient separately (median $R^2$).
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. We tested for differences in AUC values between Tmax from this study and nondeconvolved TTP, as well as other PW maps from a previous study using the Mann–Whitney rank-sum test. Statistical significance was set at \( P < 0.05 \).

Data were analyzed by Sigmastat 3.11 (SYSTAT Software 2004) 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 (IQR, 52–139). Twenty-five patients had a middle cerebral artery (right/left hemisphere, 8/17) and one had a right posterior cerebral artery stroke. The median NIHSS score on admission was 9 (IQR, 6–13.5). Internal carotid stenosis was present in 12 (ipsilateral) and 4 (contralateral) patients.

Part A: Regression Analysis

On visual inspection, an excellent spatial correspondence of the hypoperfused areas (as defined by PET) was found on maps of Tmax (Figure 1). The linear regression analysis showed a good and significant intra-individual dependency (mean of regression coefficients of all patients: \( R^2 = 0.636 \); SD, 0.161). In contrast, the regression analysis of the pooled data were weak \( (R^2 = 0.498) \) and did not show a linear characteristic (Figure 2).

Part B: ROC Analysis

The ROC curve analysis was performed for every patient. Representative Tmax data of 1 patient are displayed in Figure 3. The mean AUC value (indicating the best detection of PF) for Tmax was 0.95 (IQR, 0.93–0.97). Comparing this value with the AUC results from a previous study of the same patient population, this is comparable to maps of TTP and CBF, whereas maps of MTT and CBV showed significantly lower AUC values \( (P < 0.05) \). The optimal PF threshold for Tmax (median values of the individual ROC curve analysis of the 26 patients) identified by the equal sensitivity and specificity threshold (ESST) method was 5.5 seconds (IQR, 3.9–6.6 seconds), with a sensitivity of 88% (IQR, 84%–95%) and a specificity of 89% (IQR, 82%–93%). The results of a pooled ROC curve analysis were in line with these findings. See the Table for a summary of values.

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To rule out effects of the time point of imaging after stroke, patients were dichotomized according to the time of imaging after stroke onset (cut-off, 24 hours). There was no significant difference in early vs late imaging for the PF threshold values (5.6 vs 5.2; \( P = 0.902 \)) or for the AUC values (0.96 vs 0.93; \( P = 0.893 \)).

Discussion

Based on the threshold-independent AUC analysis, we found a similar performance of Tmax and TTP. This is an interesting finding because Tmax represents TTP after deconvolution. One reason might be that arterial dispersion and tissue transit time, factors that are reduced by deconvolution, could contain relevant hemodynamic information. This might explain the similar performance of nondeconvolved TTP maps. Another possible reason is the influence of the AIF used for deconvolution. Because the AIF is not uniquely

Table. Median Equal Sensitivity and Specificity Threshold Penumbra Flow Cut-off Values of Tmax, CBF, CBV, MTT, and TTP Delay With Its Corresponding Mean Sensitivity and Specificity and the Median AUC Results Derived From the Receiver-Operating Characteristic Curve Analysis

<table>
<thead>
<tr>
<th>Penumbral Flow Threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (sec)</td>
<td>5.5 (3.9–6.6)</td>
<td>0.88 (0.84–0.95)</td>
<td>0.89 (0.82–0.93)</td>
</tr>
<tr>
<td>TTP delay* (sec)</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>
</tr>
<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>
</tr>
<tr>
<td>MTT† (sec)</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>
</tr>
<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>
</tr>
</tbody>
</table>

AUC indicates area under the curve; CBF, cerebral blood flow; CBV, cerebral blood volume; Tmax, time to maximum; TTP, time to peak.

*CBF, CBV, MTT, and TTP delay are included for comparison from a previous study.
†Significantly \( (P < 0.05) \) lower AUC values (Mann–Whitney rank-sum test).

**Variation is given as interquartile range.**
defined and is subject to some dispersion in stroke pathology, it adds variability to the Tmax measure. TTP, however, might be more stable because it is normalized to a large homogeneous reference region compared to few voxels chosen in the AIF-based method. In comparison to MTT and CBV, maps of Tmax have the advantage to measure the TTP of the fraction of tracer in a voxel at any given time. This contrasts to the time the contrast bolus takes to transverse the voxel (eg, MTT) or to the AUC of the contrast bolus intensity (eg, CBV). In acute stroke, however, the exact determination of the AUC of the contrast bolus might be impaired by a bias in the arterial input in cases in which blood reaches tissue through collaterals because of vessel occlusion,22 by an extremely delayed bolus arrival,9,13 and by recirculation of contrast agent.22 Therefore, the better performance of Tmax can in part be explained by the stronger dependency of MTT and CBV from the exact determination of the area under the deconvolved tissue curve (AUC).17

Two previous stroke studies using reference methods for CBF measurement investigated the performance of Tmax. A PET study of 5 stroke patients found the diagnostic performance of Tmax similar to the nondeconvolved TTP delay and to MTT delay.10 However, this study did not perform a ROC curve analysis to determine the best PW parameter. A xenon CT study of 9 subacute and chronic stroke patients7 found the performance of Tmax PD detection to be similar to MTT, even though Tmax values correlated better than MTT values with xenon CT values of CBF. One study using MR as the reference method investigated the performance of Tmax to predict infarct growth using a ROC analysis. Compared to other PWI maps, the most predictive maps were the nondeconvolved Tmax maps.8 These findings generally agree with our results, although we found that Tmax and the nondeconvolved TTP maps were comparable.

Based on the ROC curve analysis, we found a Tmax threshold of >5.5 seconds as the best estimate of PF (sensitivity, 88%; specificity, 89%). This cut-off value is in line with a previous PET study of 5 patients with a PF threshold of >5.4 seconds, a sensitivity of 48%, and a specificity of 92%.10 Another comparative ROC curve analysis of 9 patients found a Tmax threshold of >4 seconds (sensitivity, 68%; specificity, 80%) that most accurately predicted xenon CT CBF <20 mL/100 g/min, but time between xenon CT and PWI were performed with a median delay of 12 hours (IQR, 7–19), and CBF changes might have influenced the comparison.7

There are a few studies defining Tmax-based PF thresholds by follow-up MRI as a reference method. Shih et al8 assessed a group of 14 patients with early vessel recanalization after intra-arterial thrombolytic therapy and found the initial PWI lesion volume defined by Tmax >6 to 8 seconds and strongly correlated with final infarct volume (diffusion-weighted imaging) on day 7. Because all patients received thrombolytic therapy, this threshold distinguishes core infarct from penumbra tissue rather than penumbra from benign oligemia. Therefore, a PF threshold <6 seconds has to be assumed.8 Using a volumetric seed-growing approach, Olivot et al9 presented a substudy of the DEFUSE population. In patients without early reperfusion, a Tmax threshold >4 seconds best predicted final infarct volume on FLAIR imaging on day 30.6 Overall, our findings further strengthen the belief that the Tmax PF threshold lies between >5 to 6 seconds.

Several methodical issues and limitations of our study have to be discussed. First, our imaging and postprocessing protocol influenced the calculation of absolute values, as discussed in detail previously.13 Second, because repetition time sampling leads to discretization errors in the measured Tmax, and because repetition time is typically between 1.5 and 2.5 seconds in most studies,5–8,10,17 the measure is too roughly discretized to detect very small arrival delay differences between voxels. To improve time resolution, we have chosen a rather short repetition time of 1.3 seconds.21

In summary, the performance of Tmax to detect the PF threshold in acute stroke is excellent. The PF threshold >5.5 seconds is an important finding because in recent clinical trials, including DEFUSE and EPITHET, a Tmax threshold >2 seconds was used to define critically hypoperfused tissue 3 to 6 hours after symptom onset.3,4 Regarding our data and previous studies, this threshold includes benign oligemia and seems not suitable. The optimal Tmax threshold seems at least >5 to 6 seconds to define the tissue at risk. This threshold should be implemented in future clinical stroke trials and already has been chosen in the ongoing clinical trials DEFUSE-2 and EXTEND (>6 seconds). Importantly, our data also support the use of “simple” TTP maps if postprocessing is not feasible or too time-consuming. It has to be proven whether TTP maps can replace deconvoluted measures in the future.

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Disclosures

None.

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