

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

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

J. Sobesky, MD; O. Zaro Weber, MD; F.-G. Lehnhardt, MD; V. Hesselmann, MD; A. Thiel, MD; C. Dohmen, MD; A. Jacobs, MD; M. Neveling, MD; W.-D. Heiss, MD

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 penumbra 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 ¹⁵O-water PET. In a volumetric analysis, each threshold's sensitivity, specificity, and predictive values were calculated.

Results—The median hypoperfusion volume was 34.5 cm³. 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 penumbra 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;35:2843-2847.)

Key Words: cerebral blood flow ■ magnet resonance imaging ■ perfusion ■ stroke, acute ■ tomography, emission computed

Therapeutic interventions in acute ischemic stroke depend on the presence of hypoperfused but still viable tissue.¹ Time-dependent perfusion thresholds have been established by positron emission tomography (PET) with ¹⁵O-water to distinguish hypoperfused tissue evolving toward infarction (<12 mL/min per 100 g) from penumbra flow with functionally compromised but viable tissue (12 to 20 mL/100 g per min).^{1,2} These results were one of the major driving forces in developing today's concept of stroke management, but PET measurements are restricted to few centers. In the past years, the increasing availability of diffusion-weighted (DW) and perfusion-weighted (PW) magnetic resonance imaging (MRI) has importantly enhanced acute stroke diagnosis because clinical studies and therapeutic decisions are increasingly based on MRI parameters.³⁻⁵ Time-to-peak (TTP) maps

are frequently used to estimate the ischemic compromise and to calculate the "mismatch" volume or the "tissue at risk."⁶⁻¹⁰ This important role of PWI emphasizes the need for a validation in a clinically relevant setting. We therefore performed multimodal imaging with PW-MRI and PET in acute human stroke comparing TTP maps with ¹⁵O-water PET. Different TTP thresholds were compared with PET-derived cerebral blood flow (CBF) to identify the best estimate of hypoperfusion < 20 mL/100 g per minute.

Patients and Methods

Imaging

Eleven acute stroke patients were included in our prospective study. After informed consent, MR and PET scanning was performed under

Received July 31, 2004; final revision received September 9, 2004; accepted September 15, 2004.

From the Max Planck Institute for Neurological Research (J.S., O.Z.W., A.T., C.D., A.J., W.-D.H.), Cologne, Germany; the Departments of Neurology (J.S., O.Z.W., F.-G.L., A.T., C.D., A.J., M.N., W.-D.H.) and Diagnostic Radiology (V.H.), University of Cologne, Germany.

Correspondence to Dr Jan Sobesky, Department of Neurology, University of Cologne, Josef Stelzmannstr. 9, 50924 Köln, Germany. E-mail j.sobesky@pet.mpin-koeln.mpg.de

© 2004 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000147043.29399.f6

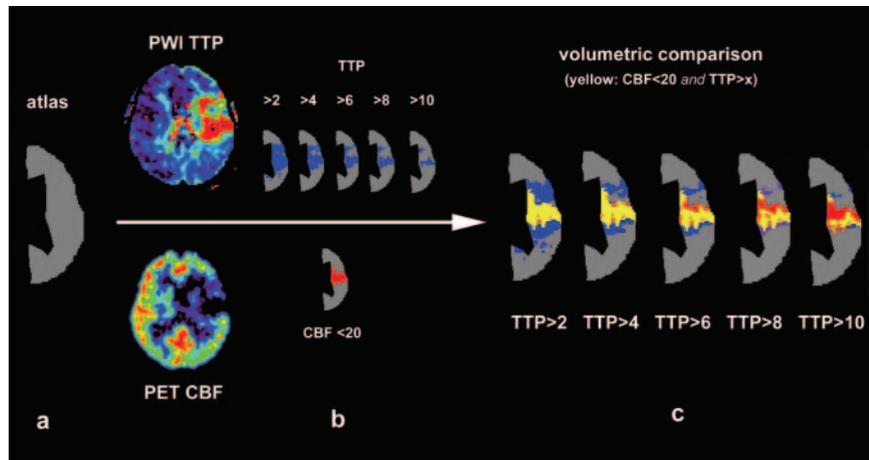


Figure 1. Volumetric comparison of the CBF and TTP compartments. Within an individual brain atlas of the affected hemisphere (a), the volume of CBF <20 mL/100 g per min (red) and the volumes of different TTP delays (blue) were generated by thresholding the respective images (b). In a volumetric comparison, 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 $<x$).

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 $3.6 \times 3.6 \times 6$ 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 ^{15}O -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.¹¹

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 pooling, 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 ($3.6 \times 3.6 \times 6.6$ mm).

Within an individual brain atlas of white and gray matter (Figure 1a), the volume of hypoperfusion <20 mL/100 g per minute was generated by a voxel-based 3-dimensional threshold. Likewise, the TTP volumes were created with increasing TTP thresholds (>2 -, >4 -, >6 -, >8 -, and >10 -second TTP delay).⁸ Hence, for every patient, 1 volume of PET hypoperfusion (CBF <20) and 5 volumes of TTP delay (TTP >2 , TTP >4 , TTP >6 , TTP >8 , TTP >10) were assessed (Figure 1b). To quantify the spatial overlap, a voxel-based volumetric comparison of CBF <20 and the TTP volumes was

TABLE 1. Individual Patient Data

Patient	Age (y)/Sex	Time		Volume of Hypoperfusion (cm ³)	NIHSS Score	Side of Ischemia	Vessel Pathology/ Degree of Stenosis (%)
		Onset of Symptom to PWI (h)	PWI to PET (min)				
1	37/F	16	130	198.0	17	RMCA, ACA	RICA/100
2	57/M	2	45	34.5	11	LMCA	LMCA/100
3	78/F	8	60	1.2	1	RMCA	RICA/100
4	45/M	18	140	362	13	RMCA, ACA	RICA/100
5	56/M	5	140	113.6	6	LMCA	LICA/100
6	62/M	4.5	60	5.0	5	LMCA	RMCA/100
7	58/F	20	60	210.2	18	LMCA, ACA	LICA/100
8	74/F	4	100	33.3	10	LMCA	LICA/70
9	55/M	1.8	20	5.3	8	LMCA	—
10	46/M	18	60	266.0	22	LMCA, ACA	LMCA/100
11	53/M	8	60	15.7	6	LMCA	—
Median	56	8	60	34.5	10		
Min	37	1.8	20	1.2	1		
Max	78	20	140	362.0	22		

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.

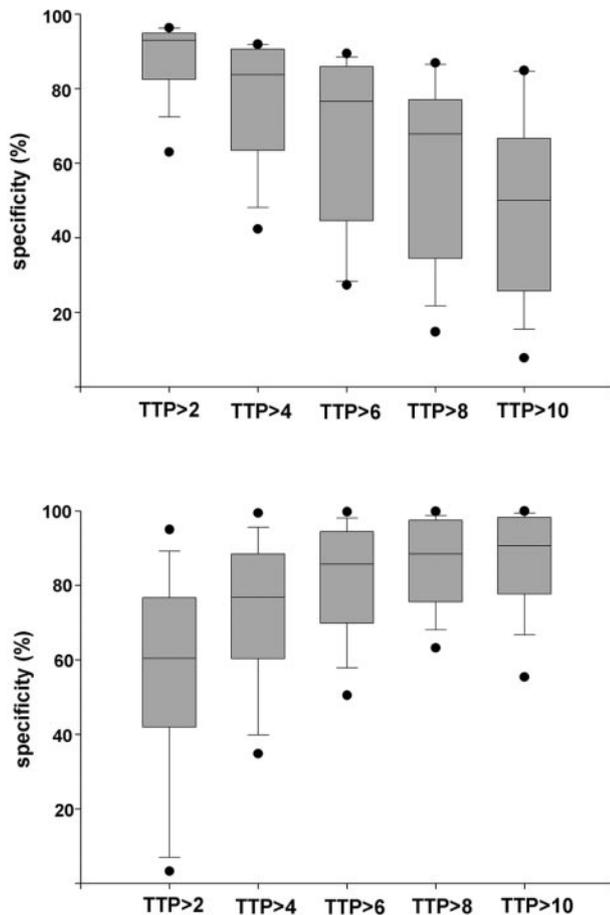


Figure 2. Sensitivity and specificity values of the different TTP thresholds for the detection of hypoperfusion <20 mL/100 g per min. Values are given as the median (line), 25th/75th percentile (box plot), 10th/90th percentile (bars), and range (black circles).

performed and the subcompartments (Figure 1c) were used to calculate the sensitivity, specificity, and predictive values for the detection of CBF <20 .

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 Sigmasat 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 . Hence, the specificity improved for TTP >4 and TTP >6 (77% and 86%, respectively) with good to moderate sensitivity (84% for TTP >4 and 77% for TTP >6 , respectively). A further increase of the TTP threshold (ie, TTP >8 and TTP

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

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

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.

>10 seconds) identified a large part of normoperfused tissue correctly as normal on TTP imaging and had a high specificity (88% for TTP >8 and 90% for TTP >10). However, these higher thresholds missed a considerable portion of hypoperfusion and had a low sensitivity (68% for TTP >8 and 50% for TTP >10). The differences of specificity and sensitivity values for the TTP thresholds were statistically significant ($P<0.05$; except for specificity TTP >8 versus TTP >10). There was no significant correlation with hypoperfusion size or the time delay (system onset to imaging or MRI to PET).

The negative predictive value was high for all TTP thresholds (median 98% for TTP >2 , continuously decreasing to 93% for TTP >10). A normal appearance on TTP maps 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 ^{15}O -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

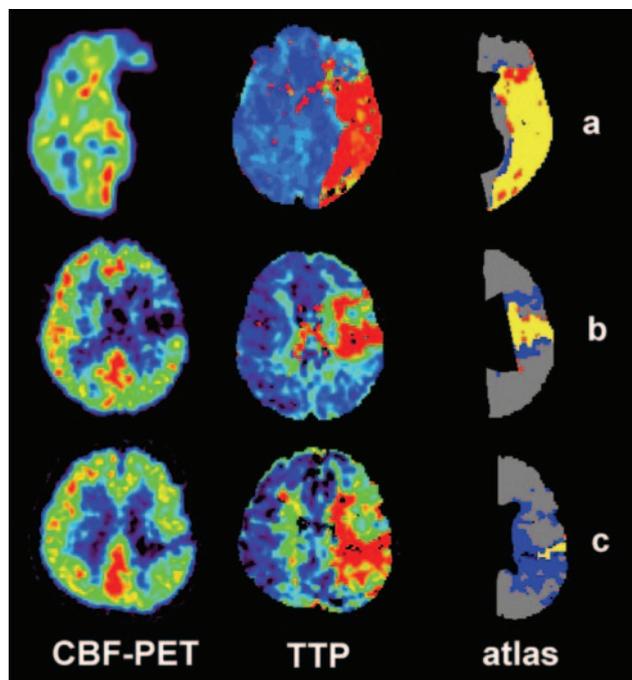


Figure 3. PET-CBF (left), TTP map (middle), and the resulting atlas for TTP >4 seconds with the respective subcompartments (right) in 3 different patients (for atlas colors see Figure 1). (a) In the case of a large MCA ischemia, a good agreement was found between PET and TTP. (b) In the example of a 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.

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,¹³ and do not rely on deconvolving algorithms, calibration with PET data, or the choice of adequate input functions.^{14,15}

Since the introduction of stroke MRI, comparative studies with single-photon emission computed tomography (SPECT)^{16,17} 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 deconvolving algorithms and correction for interindividual differences correlated with respective PET data in predefined regions of interest.^{18–20} Accordingly, an association of the TTP delay and decreased perfusion was recently described in chronic stroke patients.²¹

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^{8,9} 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.^{1,2} The correct identification of this flow threshold by TTP, combined with the extent of highly probable tissue loss indicated by DWI,²² would therefore best define 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.²³ 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 pathophysiological 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.^{8–10,13} 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 speculated²⁴ but cannot be derived from our patient sample. More important for clinical application, and in line with previous findings,^{10,15} 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.

Several methodical issues concerning the comparative imaging approach have to be addressed. According to previous studies and to the routine use of TTP maps,^{6–10} 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.

Acknowledgments

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

1. Heiss WD, Thiel A, Grond M, Graf R. Which targets are relevant for therapy of acute ischemic stroke? *Stroke*. 1999;30:1486–1489.
2. Baron JC. Perfusion thresholds in human cerebral ischemia: historical perspective and therapeutic implications. *Cerebrovasc Dis*. 2001;11(suppl 1):2–8.
3. Schellinger PD, Fiebich JB, Hacke W. Imaging-based decision making in thrombolytic therapy for ischemic stroke: present status. *Stroke*. 2003;34:575–583.
4. Barber PA, Parsons MW, Desmond PM, Bennett DA, Donnan GA, Tress BM, Davis SM. The use of PWI and DWI measures in the design of “proof-of-concept” stroke trials. *J Neuroimaging*. 2004;14:123–132.
5. Kidwell CS, Alger JR, Saver JL. Beyond mismatch: evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging. *Stroke*. 2003;34:2729–2735.
6. Thomalla GJ, Kucinski T, Schoder V, Fiehler J, Knab R, Zeumer H, Weiller C, Rother J. Prediction of malignant middle cerebral artery infarction by early perfusion- and diffusion-weighted magnetic resonance imaging. *Stroke*. 2003;34:1892–1899.

7. Rother J, Schellinger PD, Gass A, Siebler M, Villringer A, Fiebich JB, Fiehler J, Jansen O, Kucinski T, Schoder V, Szabo K, Junge-Hulsing GJ, Hennerici M, Zeumer H, Sartor K, Weiller C, Hacke W. Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke <6 hours. *Stroke*. 2002;33:2438–2445.
8. Neumann-Haefelin T, Wittsack HJ, Wenserski F, Siebler M, Seitz RJ, Modder U, Freund HJ. Diffusion- and perfusion-weighted MRI. The DWI/PWI mismatch region in acute stroke. *Stroke*. 1999;30:1591–1597.
9. Wittsack HJ, Ritzl A, Fink GR, Wenserski F, Siebler M, Seitz RJ, Modder U, Freund HJ. MR imaging in acute stroke: diffusion-weighted and perfusion imaging parameters for predicting infarct size. *Radiology*. 2002;222:397–403.
10. Shih LC, Saver JL, Alger JR, Starkman S, Leary MC, Vinuela F, Duckwiler G, Gobin YP, Jahan R, Villablanca JP, Vespa PM, Kidwell CS. Perfusion-weighted magnetic resonance imaging thresholds identifying core, irreversibly infarcted tissue. *Stroke*. 2003;34:1425–1430.
11. Heiss WD, Grond M, Thiel A, Ghaemi M, Sobesky J, Rudolf J, Bauer B, Wienhard K. Permanent cortical damage detected by flumazenil positron emission tomography in acute stroke. *Stroke*. 1998;29:454–461.
12. Cizek J, Herholz K, Vollmar S, Schrader R, Klein J, Heiss WD. Fast and robust registration of PET and MR images of human brain. *Neuroimage*. 2004;22:434–442.
13. Grandin CB, Duprez TP, Smith AM, Oppenheim C, Peeters A, Robert AR, Cosnard G. Which MR-derived perfusion parameters are the best predictors of infarct growth in hyperacute stroke? Comparative study between relative and quantitative measurements. *Radiology*. 2002;223:361–370.
14. Thijs VN, Somford DM, Bammer R, Robberecht W, Moseley ME, Albers GW. Influence of arterial input function on hypoperfusion volumes measured with perfusion-weighted imaging. *Stroke*. 2004;35:94–98.
15. Yamada K, Wu O, Gonzalez RG, Bakker D, Ostergaard L, Copen WA, Weisskoff RM, Rosen BR, Yagi K, Nishimura T, Sorensen AG. Magnetic resonance perfusion-weighted imaging of acute cerebral infarction: effect of the calculation methods and underlying vasculopathy. *Stroke*. 2002;33:87–94.
16. Karonen JO, Vanninen RL, Liu Y, Ostergaard L, Kuikka JT, Nuutinen J, Vanninen EJ, Partanen PL, Vainio PA, Korhonen K, Perkio J, Roivainen R, Sivenius J, Aronen HJ. Combined diffusion and perfusion MRI with correlation to single-photon emission CT in acute ischemic stroke. Ischemic penumbra predicts infarct growth. *Stroke*. 1999;30:1583–1590.
17. Liu Y, Karonen JO, Vanninen RL, Ostergaard L, Roivainen R, Nuutinen J, Perkio J, Kononen M, Hamalainen A, Vanninen EJ, Soimakallio S, Kuikka JT, Aronen HJ. Cerebral hemodynamics in human acute ischemic stroke: a study with diffusion- and perfusion-weighted magnetic resonance imaging and SPECT. *J Cereb Blood Flow Metab*. 2000;20:910–920.
18. Ostergaard L, Johannsen P, Host-Poulsen P, Vestergaard-Poulsen P, Asboe H, Gee AD, Hansen SB, Cold GE, Gjedde A, Gyldensted C. Cerebral blood flow measurements by magnetic resonance imaging bolus tracking: comparison with [(15)O]H₂O positron emission tomography in humans. *J Cereb Blood Flow Metab*. 1998;18:935–940.
19. Lin W, Celik A, Derdeyn C, An H, Lee Y, Videen T, Ostergaard L, Powers WJ. Quantitative measurements of cerebral blood flow in patients with unilateral carotid artery occlusion: a PET and MR study. *J Magn Reson Imaging*. 2001;14:659–667.
20. Mihara F, Kuwabara Y, Tanaka A, Yoshiura T, Sasaki M, Yoshida T, Masuda K, Matsushima T. Reliability of mean transit time obtained using perfusion-weighted MR imaging: comparison with positron emission tomography. *Magn Reson Imaging*. 2003;21:33–39.
21. Kajimoto K, Moriwaki H, Yamada N, Hayashida K, Kobayashi J, Miyashita K, Naritomi H. Cerebral hemodynamic evaluation using perfusion-weighted magnetic resonance imaging: comparison with positron emission tomography values in chronic occlusive carotid disease. *Stroke*. 2003;34:1662–1666.
22. Heiss WD, Sobesky J, Smekal U, Kracht LW, Lehnhardt FG, Thiel A, Jacobs AH, Lackner K. Probability of cortical infarction predicted by flumazenil binding and diffusion-weighted imaging signal intensity: a comparative positron emission tomography/magnetic resonance imaging study in early ischemic stroke. *Stroke*. 2004;35:1892–1898.
23. Coutts SB, Simon JE, Tomanek AI, Barber PA, Chan J, Hudon ME, Mitchell JR, Frayne R, Eliasziw M, Buchan AM, Demchuk AM. Reliability of assessing percentage of diffusion-perfusion mismatch. *Stroke*. 2003;34:1681–1683.
24. Neumann-Haefelin T, Wittsack HJ, Fink GR, Wenserski F, Li TQ, Seitz RJ, Siebler M, Modder U, Freund HJ. Diffusion- and perfusion-weighted MRI: influence of severe carotid artery stenosis on the DWI/PWI mismatch in acute stroke. *Stroke*. 2000;31:1311–1317.

Which Time-to-Peak Threshold Best Identifies Penumbra Flow?: A Comparison of Perfusion-Weighted Magnetic Resonance Imaging and Positron Emission Tomography in Acute Ischemic Stroke

J. Sobesky, O. Zaro Weber, F.-G. Lehnhardt, V. Hesselmann, A. Thiel, C. Dohmen, A. Jacobs, M. Neveling and W.-D. Heiss

Stroke. 2004;35:2843-2847; originally published online October 28, 2004;

doi: 10.1161/01.STR.0000147043.29399.f6

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2004 American Heart Association, Inc. All rights reserved.

Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/35/12/2843>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>