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Optimal Tmax Threshold for Predicting Penumbra Tissue in Acute Stroke

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Background and Purpose—We sought to assess whether the volume of the ischemic penumbra can be estimated more accurately by altering the threshold selected for defining perfusion-weighting imaging (PWI) lesions.

Methods—DEFUSE is a multicenter study in which consecutive acute stroke patients were treated with intravenous tissue-type plasminogen activator 3 to 6 hours after stroke onset. Magnetic resonance imaging scans were obtained before, 3 to 6 hours after, and 30 days after treatment. Baseline and posttreatment PWI volumes were defined according to increasing Tmax delay thresholds (>2, >4, >6, and >8 seconds). Penumbra salvage was defined as the difference between the baseline PWI lesion and the final infarct volume (30-day fluid-attenuated inversion recovery sequence). We hypothesized that the optimal PWI threshold would provide the strongest correlations between penumbra salvage volumes and various clinical and imaging-based outcomes.

Results—Thirty-three patients met the inclusion criteria. The correlation between infarct growth and penumbra salvage volume was significantly better for PWI lesions defined by Tmax >6 seconds versus Tmax >2 seconds, as was the difference in median penumbra salvage volume in patients with a favorable versus an unfavorable clinical response. Among patients who did not experience early reperfusion, the Tmax >4 seconds threshold provided a more accurate prediction of final infarct volume than the >2 seconds threshold.

Conclusions—Defining PWI lesions based on a stricter Tmax threshold than the standard >2 seconds delay appears to provide more a reliable estimate of the volume of the ischemic penumbra in stroke patients imaged between 3 and 6 hours after symptom onset. A threshold between 4 and 6 seconds appears optimal for early identification of critically hypoperfused tissue. (*Stroke*. 2009;40:469-475.)

Key Words: magnetic resonance imaging ■ perfusion-weighted imaging ■ acute brain infarct ■ thrombolysis

The ischemic penumbra is critically hypoperfused tissue that can be salvaged from infarction by early reperfusion after acute ischemia.^{1,2} If early reperfusion or a successful neuroprotective intervention does not occur, the core of the infarct will expand and the penumbra will be incorporated into the final infarct volume. Successful interventions can lead to penumbra salvage. Therefore, salvage of the penumbra is the counterpart of infarct expansion.³ Penumbra salvage integrates the effects of early reperfusion with other critical factors that influence the fate of hypoperfused tissue, such as the time elapsed since the onset of ischemia, the severity of cerebral blood flow reduction, and the presence of collateral blood flow.⁴

A technique to perform reliable, accurate, and rapid identification of the ischemic penumbra in human acute stroke patients would be highly desirable. Multimodal magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) has demon-

strated the presence of severe cytotoxic ischemic injury within minutes, which provides an estimate of the ischemic core,^{5,6} and perfusion-weighted imaging (PWI) provides an assessment of cerebral hemodynamics.⁷ The PWI/DWI mismatch hypothesis postulates that the difference between the acute PWI and DWI lesions provides an estimate of the ischemic penumbra.

Multimodal MRI estimates infarct growth by comparing the early ischemic lesion on DWI to the final infarct volume, typically assessed by the fluid-attenuated inversion recovery (FLAIR) sequence. Both the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) studies demonstrated strong associations between recanalization, reperfusion, reduced infarct growth, and favorable clinical response (FCR) in patients with a perfusion/diffusion mismatch treated with intravenous tissue-type plasminogen activator (tPA) within 3 to 6 hours of symptom onset.⁸⁻¹⁰

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How accurate is estimation of the ischemic penumbra provided by PWI/DWI techniques? An important shortcoming of bolus contrast PWI techniques is that they may overestimate critically hypoperfused tissue.^{11–13} Areas of benign oligemia that will survive, regardless of the presence or absence of reperfusion, may be included within the PWI lesion.¹⁴ A technique to reduce the volume of benign oligemia included within the PWI lesion is use of a threshold to exclude areas with minimal delay in contrast arrival times. For example, in an acute stroke patient, the volume of tissue with a Tmax delay of 2 seconds is typically larger than the volume with a delay of 4 or 6 seconds. An important challenge is to clarify which PWI thresholds most accurately estimate the volume of critically hypoperfused tissue.^{15,16}

The optimal Tmax threshold for identifying critically hypoperfused tissue is unclear. A small study of 5 acute stroke patients imaged back-to-back with PWI and positron emission tomography found that a Tmax delay between 4 and 6 seconds (5.5 seconds) was the most accurate threshold for identification of penumbral tissue.¹² Another recent study showed that a Tmax delay of 4 seconds was correlated best with cerebral blood flow values <20 mL/100 g per min as assessed by xenon computed tomography.¹⁷

To help clarify the Tmax threshold that most accurately identifies the ischemic penumbra, we examined the data from the DEFUSE study and assessed the relations between PWI volumes and both final infarct volumes and clinical outcomes. We calculated the volume of penumbra salvage (the difference between predicted final infarct volume based on the initial PWI scan and actual final infarct volume) with 4 prespecified Tmax thresholds. We hypothesized that the optimal Tmax threshold would have the following characteristics: (1) patients with an FCR would have a significantly larger volume of penumbra salvage than patients without an FCR; (2) patients with a PWI/DWI mismatch would have significantly larger penumbra salvage volumes compared with no-mismatch patients; (3) patients who experienced early reperfusion would have larger volumes of penumbra salvage compared with patients who did not reperfuse; furthermore, the baseline penumbra salvage volume should approach zero in the patients who did not reperfuse; and (4) there would be a significant negative correlation between penumbra salvage and infarct growth.

Subjects and Methods

Patients

The inclusion criteria, study design, and primary results of the DEFUSE trial have been previously reported.⁸ In brief, patients with acute ischemic stroke and a National Institute of Health Stroke Scale score (NIHSS) >5 were treated with tPA, 0.9 mg/kg IV, 3 to 6 hours after symptom onset. Participating patients underwent an MRI of the brain before tPA treatment as well as 3 to 6 hours afterward and 1 month afterward. Neurologic deficits were evaluated before tPA therapy, at the time of the second (3 to 6 hours after tPA) MRI scan, and at 30 and 90 days. An FCR was defined as an NIHSS of 0 to 1 or ≥8 points of improvement between baseline and 30 days.

MRI Protocol

DWI was performed with a spin echo–echoplanar imaging sequence (field of view=240 mm, repetition time=5 seconds, echo time=minimum allowed, slice thickness=5 mm, number of slices=19, slice gap=1 mm, acquisition matrix=128×128) and lesion volumes determined by a semiautomated thresholding algo-

rithm, which identified regions of high signal intensity that exceeded a region in the contralateral frontal lobe by >3 standard deviations. Dynamic susceptibility PWI was performed with gradient echo–echoplanar imaging (field of view=240 mm, repetition time=2 seconds, echo time=60 ms, slice thickness=7 mm, number of slices=12, slice gap=0, acquisition matrix=128×128, dynamic scans=40), and maps of the time to peak of the residue function (ie, Tmax) were generated by deconvolution of the tissue concentration over time curve with use of an arterial input function from the contralateral middle cerebral artery. The prespecified Tmax delays used to quantify the hypoperfusion on PWI were >2, >4, >6, and >8 seconds. Perfusion/diffusion mismatch was defined as a PWI lesion that was 10 cm³ larger and ≥120% of the DWI lesion volume. The “no mismatch” profile was defined as a PWI volume <120% of DWI. The “small lesion” profile was defined as baseline DWI and PWI volumes that were both <10 cm³. The “malignant” profile was defined as DWI or Tmax >8 seconds lesion volume >100 cm³. The mismatch patients without a malignant profile were classified as “target mismatch.” Early reperfusion was defined on the basis of a PWI scan performed 4 to 6 hours after initiation of intravenous tPA therapy. A PWI volume that was at least 30% less than the initial PWI volume qualified as reperfusion.

For the current substudy, we redefined the perfusion/diffusion mismatch groups according to 4 prespecified Tmax thresholds (>2, >4, >6, and >8 seconds). Penumbra salvage and infarct growth were calculated for each patient. Penumbra salvage was defined as the difference between baseline PWI lesion and final infarct volumes from each of the 4 Tmax thresholds. Infarct growth was defined as the difference between baseline DWI lesion and final infarct volume. The presence or absence of early reperfusion (a >30% reduction in PWI volume) was determined for each patient from each of the 4 prespecified Tmax thresholds as previously described.⁸ Patients with the small-lesion profile (n=18), those with technically inadequate initial (n=9) or early follow-up (n=3) PWI imaging results, and patients missing 30-day follow-up scans (n=11) were excluded from this substudy.

Statistical Analysis

We calculated descriptive statistics to describe groups as mean±SD, median with interquartile range, and proportions. We compared volumes in the groups of patients by the Mann–Whitney *U* test. We compared volumes defined by increasing Tmax delays by the Wilcoxon signed-rank test. The McNemar test was used to compare proportions of mismatch cases and reperfusion rates according to Tmax delay. We calculated Spearman’s correlations to measure associations between infarct growth and penumbra salvage volumes and compared the correlations calculated for the 4 different Tmax thresholds from *t* tests.¹⁸ We used *P*<0.05 level for statistical significance. Statistical analysis was done with SPSS 16.0 (SPSS, Inc, Chicago, Ill).

Results

General Characteristics

Thirty-three patients met the inclusion criteria (Figure 1 and Table 1.) The mean age was 69 years and the baseline median NIHSS was 13. The median time to treatment with intravenous tPA was 317 minutes, and the median baseline DWI lesion volume was 12 cm³. Increasing the Tmax delay threshold required for definition of a mismatch led to a significant decrease in the baseline PWI and penumbra salvage volumes (Figure 2). Baseline PWI volume and penumbra salvage volumes defined by Tmax >6 seconds and >8 seconds were significantly smaller (*P*<0.05) than the corresponding volumes defined by Tmax >2 seconds.

Increasing the Tmax delay threshold required for definition of a mismatch resulted in a lower percentage of patients being classified as having a mismatch but did not significantly alter the percentage classified as having early reperfusion. The

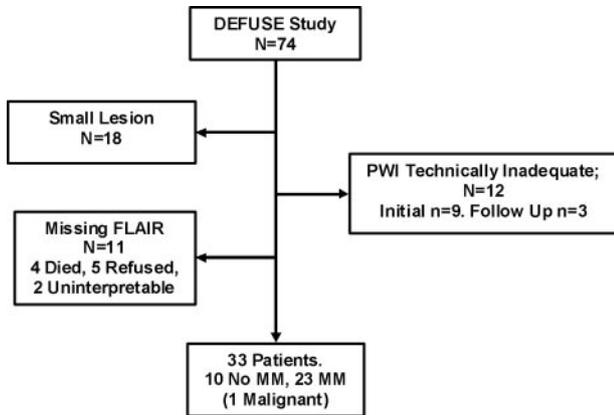


Figure 1. Flow chart for the study.

numbers of mismatch patients gradually decreased from 70% with the Tmax threshold of >2 to 24% with the >8 seconds threshold. The percentage of patients with a mismatch defined by the >6 and >8 seconds thresholds was significantly lower compared with the >2-second threshold ($P=0.031$ and $P<0.001$, respectively). The rate of early reperfusion was not significantly different among the 4 Tmax thresholds (51% for Tmax >2 and 4 seconds delay and 48% for Tmax >6 and >8 seconds delay).

Hypothesis 1: Patients With an FCR Would Have a Significantly Larger Volume of Penumbra Salvage Than Patients Without an FCR

Among all 33 patients, an FCR occurred in 45%. The final infarct volume was significantly smaller among the patients who experienced an FCR than among those who did not. An FCR was associated with a significant increase in penumbra salvage volume with the Tmax >6 or >8 seconds threshold. There was no significant association for Tmax delays of >2 or >4 seconds. For the Tmax >6 seconds threshold, the median penumbra salvage volume was 7 cm³ in patients with a favorable outcome compared with -16 cm³ for patients who did not have an FCR. (A negative value for penumbra salvage indicates that the final infarct volume is larger than the baseline PWI volume) (Table 2).

Hypothesis 2: Patients With a PWI/DWI Mismatch Would Have Significantly Larger Penumbra Salvage Volumes Compared With No-Mismatch Patients

The baseline PWI lesion volume was larger among cases with a mismatch than among cases without a mismatch, The penumbra salvage volume was significantly larger among patients with a mismatch compared with cases with no mismatch for all Tmax thresholds except the >8 seconds threshold (Table 2).

Hypothesis 3: Patients Who Experienced Early Reperfusion Would Have Larger Volumes of Penumbra Salvage Compared With Patients Who Did Not Reperfuse, and the Baseline Penumbra Salvage Volume Should Approach Zero in the No-Reperfusion Patients

The volume of penumbra salvage was increased among patients with early reperfusion when PWI volumes were defined by the

Table 1. Baseline Characteristics

	Penumbra Salvage Study (N=33)
Mean age, (SD), y	69 (3)
White, %	85
Hypertension, %	55
Diabetes, %	30
Smoking, %	45
Hyperlipidemia, %	27
Cardiac disease, %	42
History of stroke, transient ischemic attack, %	12
Median NIHSS at baseline (IQR)	13 (9, 16)
Median time to first MRI (IQR), min	283 (260, 306)
Median time to treatment (IQR), min	317 (295, 348)
Median baseline DWI volume (IQR), cm ³	12 (7, 26)
Median baseline PWI >2 seconds volume (IQR), cm ³	65 (36, 87)
Median baseline PWI >4 seconds volume (IQR), cm ³	44 (19, 71)
Median baseline PWI >6 seconds volume (IQR), cm ³	27 (10, 55)
Median baseline PWI >8 seconds volume (IQR), cm ³	17 (6, 38)
Median final infarct (30-day FLAIR) volume (IQR), cm ³	30 (13, 62)

IQR indicates interquartile range.

Tmax >6 and >8 seconds thresholds (Table 2). Early reperfusion was not significantly associated with penumbra salvage volume when initial and follow-up PWI lesion volumes were defined by the Tmax >2 seconds threshold and was of borderline significance ($P=0.08$) with the >4 seconds threshold.

For patients who did not experience early reperfusion, the >2 seconds PWI lesion volume tended to overestimate final infarct volume (median infarct volume on FLAIR was 15 cm³ smaller than baseline PWI volume), whereas the >6 and >8 seconds volumes tended to underestimate final infarct size. The median >4 seconds baseline PWI volume was very similar to the final infarct volume in patients who did not have reperfusion (median volume was 1 cm³ larger than final infarct volume). The difference in median penumbra salvage volumes in the patients with no reperfusion was statistically different for the >2 seconds versus >4 seconds thresholds ($P<0.0001$). See Figure 2 for a representative case.

Hypothesis 4: There Would Be a Significant Negative Correlation Between Penumbra Salvage and Infarct Growth

We estimated the correlation between infarct growth and penumbra salvage volumes defined by increasing Tmax delay thresholds (Table 3). A statistically significant negative correlation was documented for all thresholds tested, and the strength of the correlation increased significantly for higher Tmax thresholds. The correlation coefficients for the Tmax >6 and >8 seconds thresholds were significantly stronger than for the >2 seconds threshold ($P<0.001$).

Discussion

If the PWI/DWI mismatch provides an accurate estimate of the volume of penumbral tissue in acute stroke patients, then there should be an inverse relation between penumbra salvage

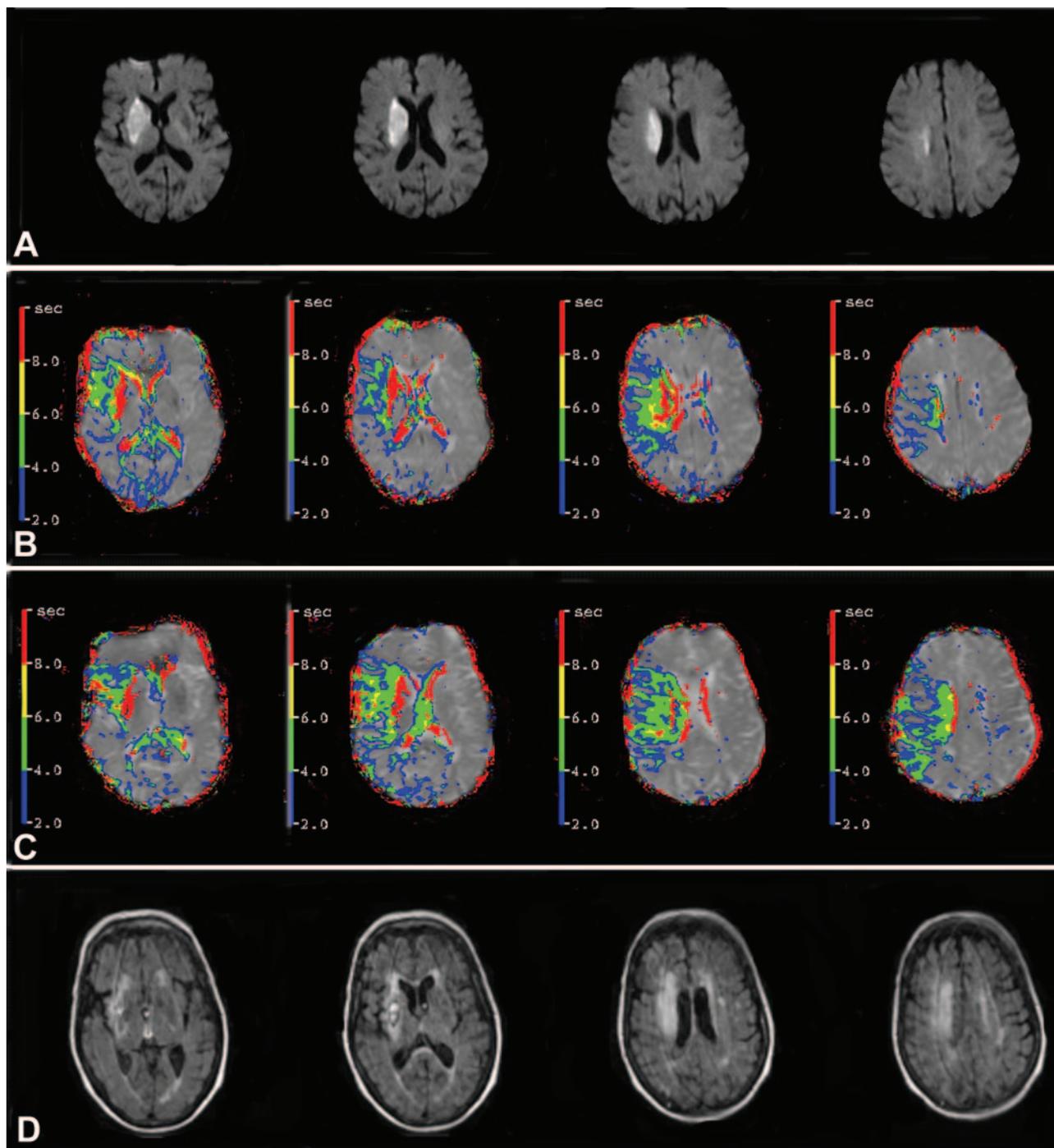


Figure 2. Illustration of the evolution of PWI lesion volumes according to Tmax delay. The patient, a 79-year-old woman, was treated with intravenous tPA 340 minutes after symptom onset. She did not experience an FCR. Baseline MRI was performed 302 minutes after symptom onset; the first follow-up MRI was 270 minutes after the start of treatment, and the final MRI was 27 days after symptom onset. Tmax color scale: 2 seconds T_{max} ≤ 4 seconds (blue); 4 seconds T_{max} ≤ 6 seconds (green); 6 seconds T_{max} ≤ 8 seconds (yellow); 8 seconds T_{max} (red). A, On baseline DWI, lesion volume was 15 cm³. B, On baseline PWI, lesion volumes according to Tmax delay were as follows: Tmax > 2 seconds = 67 cm³; > 4 seconds, 34 cm³; > 6 seconds, 12 cm³; and > 8 seconds, 9 cm³. C, On follow-up PWI, lesion volumes according to Tmax delay were as follows: > 2 seconds, 97 cm³; > 4 seconds, 57 cm³; > 6 seconds, 17 cm³; and > 8 seconds, 13 cm³. D, On final FLAIR, final infarct volume was 24 cm³.

and infarct growth regardless of the presence or absence of reperfusion. For patients who do not experience reperfusion, substantial infarct growth and minimal penumbra salvage is expected. In contrast, for patients with successful early reperfusion, minimal infarct growth and substantial penumbra salvage is expected. On the basis of this premise, we assessed

the relations between penumbra salvage and both clinical and imaging outcomes in an attempt to determine which Tmax threshold provides the most accurate estimate of critically hypoperfused brain tissue.

We hypothesized that the optimal threshold would provide the strongest correlations between penumbra salvage and

Table 2. Penumbra (P) Salvage and Baseline PWI Volumes Based on Tmax Delay

Comparison of MRI Volumes in Patients With an FCR vs No FCR			
	FCR Median Volume (IQR), n=15	No FCR Median Volume (IQR), n=18	P*
Baseline DWI	+10 (+7, +42)	+13.5 (+5, +22)	0.71
Baseline PWI >2 seconds	+70 (+46, +83)	+56 (+29, +102)	0.90
Baseline PWI >4 seconds	+54 (+35, +50)	+39 (+11, +83)	0.79
Baseline PWI >6 seconds	+30 (+20, +52)	+26 (+5, +55)	0.56
Baseline PWI >8 seconds	+22 (+9, +39)	+13 (+4, +38)	0.44
30-day FLAIR	+13 (+8, +43)	+39 (+23, +72)	0.03
P salvage >2 seconds	+41(+12, +60)	+14 (-15, +43)	0.21
P salvage >4 seconds	+18 (+7, +37)	0 (-27, +21)	0.12
P salvage >6 seconds	+7 (-1, +22)	-16 (-47, -2)	0.02
P salvage >8 seconds	+5 (-7, +9)	-20 (-49, -5)	<0.01

Comparison of MRI Volumes in Patients With Mismatch vs No Mismatch Based on the Tmax Thresholds Used to Determine PWI Volumes			
Tmax Threshold	Mismatch Patients, n; Median Volume, cm ³ (IQR)	No-Mismatch Patients, n; Median Volume, cm ³ (IQR)	P*
>2 seconds	n=23	n=10	
Baseline DWI	+10 (+4, +18)	+24 (+16, +65)	0.05
Baseline PWI >2 seconds	+70 (+49, +98)	+25 (+12, +66)	0.01
30-day FLAIR	+24 (+11, +55)	+45 (+24, +73)	0.13
P salvage >2 seconds	+42 (+21, +63)	-14 (-28, +3)	<0.01
>4 seconds	n=21	n=12	
Baseline DWI	+10 (+3, +18)	+21 (+9, +62)	0.06
Baseline PWI >4 seconds	+55 (+37, +83)	+11 (+8, +49)	<0.01
30-day FLAIR	+24 (+11, +60)	+34 (+21, +72)	0.33
P salvage >4 seconds	+27 (+10, +42)	-18 (-36, +1)	<0.01
>6 seconds	n=17	n=16	
Baseline DWI	+10 (+8, +24)	+17 (+6, +43)	0.33
Baseline PWI >6 seconds	+46 (+28, +59)	+9 (+3, +26)	<0.01
30-day FLAIR	+23 (+11, +60)	+34 (+21, +72)	0.34
P salvage >6 seconds	+17 (-3, +25)	-22 (-43, -2)	<0.01
>8 seconds	n=8	n=25	
Baseline DWI	+11 (+6, +24)	+15 (+7, +26)	0.55
Baseline PWI >8 seconds	+47 (+25, +58)	+11 (+4, +25)	0.01
30-day FLAIR	+51 (+18, +63)	+25 (+11, +55)	0.50
P salvage >8 seconds	+4 (-7, +12)	-13 (-33, 0)	0.50

Comparison of MRI Volumes in Patients With Early Reperfusion vs No Early Reperfusion Based on the Tmax Threshold Used to Determine PWI Volumes			
Tmax Threshold	Early Reperfusion, n; Median Volume, cm ³ (IQR)	No Early Reperfusion, n; Median Volume, cm ³ (IQR)	P*
>2 seconds	n=17	n=16	
Baseline DWI	+16 (+8, +24)	+11 (+5, +28)	0.96
Baseline PWI >2 seconds	+63 (+43, +86)	+65 (+32, +99)	0.90
30-day FLAIR	+19 (+9, +62)	+38 (+25, +66)	0.06
P salvage >2 seconds	+41 (+3, +57)	+15 (-19, +39)	0.28
>4 seconds	n=17	n=16	
Baseline DWI	+16 (+8, +24)	+11 (+6, +28)	0.93
Baseline PWI >4 seconds	+52 (+33, +58)	+36 (+9, +84)	0.17
30-day FLAIR	+21 (+10, +62)	+38 (+24, +66)	0.50
P salvage >4 seconds	+21 (+9, +33)	+1 (-28, +11)	0.08

(Continued)

Table 2. Continued

Tmax Threshold	Comparison of MRI Volumes in Patients With Early Reperfusion vs No Early Reperfusion Based on the Tmax Threshold Used to Determine PWI Volumes		P*
	Early Reperfusion, n; Median Volume, cm ³ (IQR)	No Early Reperfusion, n; Median Volume, cm ³ (IQR)	
>6 seconds	n=16	n=17	
Baseline DWI	+12 (+5, +31)	+12 (+10, +26)	0.82
Baseline PWI >6 seconds	+27 (+21, +52)	+20 (+4, +55)	0.31
30-day FLAIR	+20 (+8, +63)	+35 (+24, +60)	0.07
P salvage >6 seconds	+5 (-3, +22)	-20 (-40, +2)	0.03
>8 seconds	n=16	n=17	
Baseline DWI	+12 (+3, +31)	+12 (+10, +26)	0.63
Baseline PWI >8 seconds	+20 (+11, +33)	+9 (+3, +44)	0.24
30-day FLAIR	+22 (+9, +63)	+32 (+24, +60)	0.24
P salvage >8 seconds	+2 (-17, +11)	-21 (-33, 0)	0.04

Baseline PWI >2 seconds=baseline PWI volume defined by Tmax >2 seconds; P salvage >2 seconds=penumbra salvage calculated from baseline PWI volume defined by Tmax >2 seconds.

*Nonparametric Mann-Whitney test.

various clinical and imaging-based outcomes. All 4 of the hypotheses tested revealed significant correlations among 1 or more of the Tmax thresholds tested. However, the higher thresholds (>4, >6, or >8 seconds) outperformed the Tmax threshold of >2 seconds on virtually all assessments. These findings are important because the Tmax >2-second threshold has been selected to define PWI lesions in several clinical studies, including DEFUSE and EPITHET.^{8,9}

We found that penumbra salvage volume defined by a Tmax >6 seconds delay was significantly increased in patients with favorable outcomes, in patients who experienced reperfusion, and among mismatch patients. No other threshold was significant for all 3 of these assessments. In addition, the correlation between infarct growth and penumbra salvage volumes defined by Tmax >6 seconds was significantly higher than that for Tmax >2 seconds, as was the difference in median penumbra salvage volume in patients with a favorable versus an unfavorable clinical response. These findings all suggest that Tmax >6 seconds provides a more accurate estimate of critically hypoperfused tissue compared with a Tmax of >2 seconds.

It appears that baseline Tmax lesions >2 seconds overestimate the volume of penumbral tissue. For example, even among patients without reperfusion, a Tmax >2 seconds

identified a median penumbra salvage of 15 cm³ (the final infarct volume was a median of 15 cm³ smaller than predicted by the baseline PWI), as illustrated in Figure 2. The >4 seconds threshold most closely predicted final infarct volume in patients who did not reperfuse. For the stricter thresholds (>6 and >8 seconds), final infarct volume was often larger than predicted in patients who did not reperfuse. These findings suggest that the stricter thresholds (>6 and >8 seconds) may underestimate the volume of critically hypoperfused tissue and imply that a threshold in the range of 4 to 6 seconds provides the best early estimation of critically hypoperfused tissue. These findings correspond well with a recently published positron emission tomography study that suggested that a Tmax delay of 5.5 seconds was the optimal threshold for identification of penumbral tissue.¹² Our findings are also supported by a xenon computed tomography study in subacute stroke patients that found that regions with a cerebral blood flow of <20 mL/100 g per min corresponded best with Tmax values of >4 seconds.¹⁷

A previous MRI study assessed a group of patients who had early recanalization after intra-arterial therapy and demonstrated that the pretreatment PWI lesion volume defined by a Tmax \geq 6 seconds threshold was strongly correlated with final infarct volume.⁷ We were unable to confirm this finding in the DEFUSE dataset. Our data demonstrate a strong correlation between baseline DWI lesion volume and final infarct volume among patients with early reperfusion; however, the baseline PWI volumes did not demonstrate significant correlations, irrespective of the threshold chosen. We suspect that this was so because even severe Tmax delays do not necessarily cause irreversible injury if effective reperfusion occurs rapidly.

Our results suggest that selecting a more severe Tmax threshold, such as >4 or >6 seconds, could significantly improve the precision of PWI for estimating the volume of penumbral tissue in acute stroke patients and improve the accuracy of early prediction of final infarct volume. Using a stricter Tmax threshold would reduce the percentage of patients considered to have a mismatch but may identify mismatch patients who are more likely to have salvageable tissue.

Table 3. Correlation Between Infarct Growth and Penumbra Salvage Volume Based on Tmax Delay Used to Determine PWI Volume

Tmax Thresholds	All (n=33)	
	rho	P
>2 seconds	-0.38	0.03
>4 seconds	-0.47	<0.01
>6 seconds	-0.65	<0.01*
>8 seconds	-0.70	<0.01*

Rho indicates Spearman correlation coefficient.

*Significantly higher than the correlation observed between 2-second penumbra salvage and infarct growth.

The primary limitation of our study is the small sample size: only 33 of the 74 DEFUSE patients were eligible for this substudy. The small size limits interpretation of these results and our statistical power to compare the correlation coefficients. The primary reason for exclusion was the small-lesion profile (n=18). DEFUSE included consecutive patients, regardless of baseline PWI lesion volume. It was prespecified that patients with very small baseline PWI volumes were excluded from any of the DEFUSE analyses that involved assessment of reperfusion because the presence or absence of reperfusion could not be assessed for very small PWI lesions. The second most common reason for exclusion was a failure to obtain either baseline or follow-up perfusion imaging (n=12). Failure to obtain the 30-day FLAIR scan was the other common reason for exclusion. This often occurred because of death before 90 days or severe disability that precluded returning the patient to follow-up MRI. Obtaining the “final infarct volume” at an earlier time point could help reduce this limitation in future studies.

DEFUSE is an exploratory pilot study in which all patients were treated with intravenous tPA. Hence, it is impossible to separate the effects of spontaneous versus “tPA-induced” early reperfusion. The EPITHET study addressed this issue and confirmed that intravenous tPA therapy increases the rate of reperfusion among mismatch cases.⁹ Our data were collected in stroke patients initially imaged 3 to 6 hours after symptom onset. Our findings may not be applicable to patients who are evaluated at other time points.

Alternative methods to improve the definition of mismatch include requiring a larger mismatch ratio than the typically selected 1.2 or a large mismatch volume.^{19,20} Whether the use of any of these strategies will improve the accuracy for selection of patients who are most likely to benefit from therapeutic interventions is uncertain. A voxel-by-voxel analysis of coregistered scans (baseline and follow-up PWI/DWI and follow-up FLAIR) is likely to provide more accurate predictions of final infarct volume and location. These analyses from the DEFUSE study are in progress.

In conclusion, our results suggest that a Tmax threshold >4 seconds, 3 to 6 hours after stroke onset, provides the most accurate estimate of final infarct volumes in patients who do not reperfuse. Furthermore, a threshold of >4 to 6 seconds is optimal for estimating the ischemic penumbra.

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Disclosures

None.

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