Perfusion-Weighted Magnetic Resonance Imaging Thresholds Identifying Core, Irreversibly Infarcted Tissue

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Background and Purpose—Identifying core, irreversibly infarcted tissue and salvageable penumbral tissue is crucial to informed, physiologically guided decision making regarding thrombolytic and other interventional therapies in acute ischemic stroke. Pretreatment perfusion MRI offers promise as a means to differentiate core from penumbral tissues.

Methods—Diffusion-perfusion MRIs were performed before treatment and on day 7 in patients undergoing successful vessel recanalization with intra-arterial thrombolytic therapy. Perfusion maps of the time to peak of the residue function (T max) were generated after deconvolution of an arterial input function. Initial perfusion abnormalities and final infarct regions were outlined by hand. Posttreatment images were coregistered to the pretreatment study. Voxel-by-voxel and volume analyses were performed to identify thresholds of perfusion abnormalities that best predict core, irreversibly infarcted tissue.

Results—Fourteen patients (4 men, 10 women) with vessel recanalization were studied. Mean age was 73 years, and median entry National Institutes of Health Stroke Scale score was 12. Mean time from symptom onset to start of intra-arterial infusion was 245 minutes and to recanalization was 338 minutes. With a voxel-by-voxel analysis, T max ≥6 and ≥8 seconds (sensitivity, 71% and 53%; specificity, 63% and 80%) correlated most highly with day 7 final infarct. With a volume analysis, T max ≥6 and ≥8 seconds (r²=0.704 and r²=0.705) correlated most highly with day 7 final infarct.

Conclusions—Perfusion-weighted imaging measures of ischemia severity accurately differentiate irreversibly injured core from penumbral, salvageable tissue. The best threshold for identifying core infarcted tissue is adjusted T max of ≥6 to 8 seconds. (Stroke. 2003;34:1425-1430.)

Key Words: magnetic resonance imaging, perfusion-weighted stroke, acute stroke, ischemic thrombolysis

A number of clinical trials have demonstrated that intravenous and intra-arterial thrombolysis decreases rates of dependency after acute ischemic stroke if administered within 3 and 6 hours, respectively.1,2 However, many stroke patients are currently ineligible for potentially beneficial therapy because of the narrow time window available for initiation of therapy. As few as 1% to 2% of patients presenting with acute ischemic stroke in the United States receive thrombolysis.3-5 In addition, 6% to 10% of treated patients develop symptomatic hemorrhagic transformation after thrombolytic therapy. There is therefore a recognized need for novel strategies to identify patients who would most benefit from therapy, ie, patients with salvageable penumbral tissue.

Diffusion- and perfusion-weighted MRI (DWI and PWI) studies have demonstrated the ability to identify acute ischemic lesions and to predict lesion enlargement in patients who present with ischemic stroke within the first 24 hours.6-12 Acute DWI lesions depict regions of tissue bioenergetic failure caused by ischemia; PWI identifies areas of hemodynamic compromise caused by hypoperfusion. According to the diffusion-perfusion mismatch model, the ischemic penumbra is represented by the area of brain that is hypoperfused but does not yet demonstrate diffusion abnormality.13 However, there is growing evidence that the mismatch model may oversimplify the distinction of ischemic penumbra from irreversibly infarcted core. Because DWI lesions have been shown to reverse with successful thrombolysis in human patients, the mismatch model therefore overestimates the amount of irreversibly infarcted core tissue.14-17

Several prior studies have delineated perfusion thresholds that distinguish benign oligemia from ischemic penumbral tissue by determining values that predicted final infarct size in patients not being treated with thrombolysis in whom the infarct grows to consume the entire penumbra to the benign oligemia border.8,10,11 These studies could not, however, delineate perfusion thresholds that distinguish the irreversibly infarcted core from penumbral regions. Identifying core-penumbra thresholds requires analysis of predictors of final
infarct volume in patients successfully recanalized in whom the infarct is stabilized at the border of the core without transgressing into penumbral territories. Although previous studies using positron emission tomography (PET) have characterized cerebral blood flow (CBF) thresholds that predict irreversible infarct with and without thrombolysis, ours is the first study to attempt to identify MR perfusion parameters that may be more clinically applicable during the initial neuroimaging evaluation of a patient presenting with symptoms of acute stroke.18,19

The goal of the present study was to provide the first characterization of perfusion thresholds that differentiate irreversibly, infarcted core tissue from ischemic penumbral tissue in the setting of thrombolysis. We hypothesized that perfusion thresholds more severe than those identified for benign oligemia-ischemic penumbra demarcation would distinguish irreversibly infarcted core tissues from ischemic penumbra.

Subjects and Methods

Patient Selection

The present analysis was performed as part of an ongoing prospective study of diffusion-perfusion MRI changes in patients receiving intra-arterial thrombolytic therapy for acute ischemic stroke. Patients from this larger study were included in the present analysis if (1) they presented with symptoms of acute middle cerebral artery (MCA) territory ischemia with a large-vessel occlusion demonstrated at angiography, (2) they were treated with either combined intravenous/intra-arterial tPA within 3 hours of symptom onset or intra-arterial thrombolysis only within 6 hours of symptom onset, (3) partial or complete vessel recanalization was achieved, (4) a pretreatment DWI and PWI were performed, and (5) hemorrhagic transformation was not visualized on the posttreatment imaging studies to prevent distortion of measured time to peak of the residue function (T\text{max}) values.

Pure intra-arterial thrombolysis was administered with either urokinase (up to a maximum of 1 000 000 IU) or tPA (generally up to a maximum dose of 22 mg) infused at the site of the clot at the time of angiography until recanalization was achieved or until maximum dose was reached. Gentle mechanical clot disruption was also allowed at the time of the intra-arterial thrombolytic infusion. Combined intravenous/intra-arterial tPA was administered at a dose of 0.6 mg/kg IV, 10% to 15% bolus over 1 minute with the remaining dose infused over 30 minutes, followed by a 10-mg/h intra-arterial infusion until recanalization was achieved or a maximum intra-arterial dose of 22 mg was reached.20

Clinical outcome was assessed with the National Institutes of Health Stroke Scale (NIHSS) at baseline, several hours after thrombolysis coincident with repeated MRI, and on day 7. The study was approved by the UCLA Institutional Review Board, and informed consent was obtained from all patients.

MRI Methods

All patients underwent diffusion and perfusion MRI studies with a 1.5-T Siemens Vision scanner (Siemens Medical System) before treatment and at day 7. Figure 1 show PWI and DWI from 1 patient with occlusion of both anterior and posterior divisions of the left MCA. Diffusion imaging was performed with 2 levels of diffusion sensitization (b=0 and 1000 s/mm\(^2\)) acquired in the x, y, and z planes to calculate the apparent diffusion coefficient (ADC) values. DWI parameters were as follows: 5- to 7-mm slice thickness, no gap, and 17 to 20 slices. The day 7 protocol also included a fluid attenuated inversion recovery (FLAIR) sequence (repetition time [TR], 7000 ms; echo time [TE], 105 ms; inversion time [TI], 2000 ms; matrix size, 256\times256; field of view, 240 mm; slice thickness, 5 mm; gap, 2.5 mm). Perfusion MRI was performed with a timed contrast bolus passage technique (0.1 mg/kg contrast administered into an antecubital vein with a power injector at a rate of 5 cm/s). Perfusion imaging parameters were as follows: TR, 2000 ms; TE, 60 ms; 12 slices; slice thickness, 7 mm; no interslice gap; and field of view, 240 mm.

Image Processing and Data Analysis

Data analysis was carried out on a Research System IDL computer program designed for analysis of diffusion and perfusion data. For both volume and voxel-by-voxel analyses, voxels with ADC values >1200 \(\mu\text{m}^2/\text{s}\) were excluded to avoid cerebrospinal fluid artifact. Maps of T\text{max} were generated by deconvolution of an arterial input function and tissue concentration curves from methods described by Ostergaard et al.21 In this study, the arterial input function was measured in the contralateral MCA.

All MRI studies were coregistered to the pretreatment study to allow a voxel-by-voxel analysis of tissue fate over time. MRI volume measures

Figure 1. PWI and DWI from an 81-year-old man with occlusion of both anterior and posterior divisions of the left MCA. PWI shows 2 areas of T\text{max} \geq 6 and \geq 8 seconds in the left frontal and posterior parietal lobes that correspond to areas of greatest day 7 DWI signal intensity.
were performed jointly by 2 investigators using an open consensus method. For each patient, PWI, DWI, and FLAIR lesion volumes were outlined by hand, with volumes calculated with a computer-assisted volumetric analysis program. The final infarct was defined as all voxels with abnormality on the day 7 DWI, the FLAIR images, or both.

**Statistical Analysis**

Two methods were used to analyze the main study goal of identifying perfusion thresholds predictive of final infarction. In a voxel-by-voxel analysis, all voxels in regions at risk of progression to infarction (all voxels with any pretreatment perfusion deficit, defined as $T_{max}$ $\geq$ 2 seconds) were combined across all patients. The perfusion thresholds that best predicted tissue infarction fate were then calculated in this population of voxels by use of receiver-operating curve analysis. In a patient-by-patient volume correlation analysis, pretreatment perfusion lesion volumes were identified for all 14 patients using all $T_{max}$ values between 2 and 20 seconds. The closest correlations between these lesion volumes and final infarct volumes in all 14 patients were then identified by calculating Spearman’s $\rho$ and by calculating goodness of fit by performing linear regression. In addition, pretreatment perfusion lesion volumes were correlated with clinical severity as measured by NIHSS pretreatment and on day 7. Statistical analysis was carried out with JMP software (SAS Inc). Discriminant analysis was carried out on voxel-by-voxel basis. Spearman rank correlation and simple linear regression were used to compare volume variables. One-way analysis of variance was used to measure mean ADC values.

**Results**

Of 31 patients enrolled in our MRI protocol between January 1998 and January 2001, 14 met full inclusion criteria. Reasons for exclusion were as follows: no perfusion imaging (4 patients), hemorrhagic transformation (5 patients), no day 7 imaging (4 patients), no recanalization (1 patient), and infarctions not involving the MCA territory (3 patients). Fully analyzed patients had vascular occlusions at the following sites: 6 patients at M1 MCA, 6 patients at M2 MCA, 1 patient at extracranial ICA and M2 MCA, and 1 patient at M3 MCA. Mean age was 73 years (range, 27 to 94 years); there were 4 men and 10 women. Median entry NIHSS score was 12 (range, 6 to 25). Mean time to MRI was 144 minutes (2.4 hours; range, 74 to 271 minutes). Mean time to start of intra-arterial thrombolytic treatment from symptom onset was 260 minutes (4.3 hours; range, 164 to 350 minutes). Mean time to recanalization from symptom onset was 333 minutes (5.6 hours; range, 243 to 490 minutes). Mean time from pretreatment MRI to achievement of recanalization was 190 minutes (3.2 hours; range, 114 to 360 minutes). Acute pretreatment DWI lesions ranged in size from 2.1 mL to 52.1 mL, with a median of 16.3 mL (the Table). Acute pretreatment PWI lesion volumes, using the minimal abnormal cutoff of $T_{max}$ $\geq$ 2 seconds, ranged in size from 6.7 mL to 181.7 mL, with a median of 69.7 mL. For 13 of the 14 patients, volume of the pretreatment PWI lesion exceeded the volume of the pretreatment DWI lesion; in the remaining patient, there was a matched PWI-DWI deficit.

**Voxel-by-Voxel Analysis**

Across all 14 patients, 254 429 voxels showed some perfusion abnormality ($T_{max}$ $\geq$ 2 seconds) and were included in further voxel-by-voxel data analysis. Among these voxels, 20.0% went on to infarction on day 7 posttreatment imaging. The receiver-operating curve for all potential threshold values of $T_{max}$ between $\geq$ 2 and $\geq$ 20 seconds in predicting which voxels would proceed to infarction on day 7 are shown in Figure 2. Figure 3 shows negative and positive predictive values for these cutoffs. The most successful threshold values were 6 and 8 seconds. An initial pretreatment $T_{max}$ value of $\geq$ 6 seconds identified 71% of voxels that went on to infarction on day 7 posttreatment imaging, whereas 63% of voxels that did not end up in infarcted regions had $T_{max}$ values $<$ 6 seconds. A $T_{max}$ value of $\geq$ 8 seconds identified 53% of voxels that proceeded to infarction at day 7, whereas 80% of voxels that did not end up in infarcted regions had $T_{max}$ values $<$ 8 seconds. Positive predictive values were low at $T_{max}$ $\geq$ 2 seconds and climbed steadily as cutoff delays increased, particularly up to $T_{max}$ $\geq$ 14 seconds. Negative predictive
values began high at $T_{\text{max}} \geq 2$ seconds and fell slowly throughout the range of perfusion delays analyzed.

**Patient-by-Patient Volume Analysis**

Of the 14 patients, 13 had pretreatment PWI lesions that were larger than pretreatment DWI lesions. Day 7 final infarct size was smaller than the pretreatment DWI lesion in 9 patients and larger than the pretreatment DWI lesion volume in 5. Correlation coefficients were high for all $T_{\text{max}}$ threshold perfusion lesion volumes and final infarct volumes. The highest was for $T_{\text{max}} \geq 2$ seconds ($r=0.776$, $P=0.004$), but strong correlations were also noted for several other values, including $T_{\text{max}} \geq 6$ seconds ($r=0.495$, $P=0.014$) and $T_{\text{max}} \geq 8$ seconds ($r=0.539$, $P=0.007$). Linear regression goodness-of-fit analyses demonstrated that $T_{\text{max}}$ values $\geq 6$ and $\geq 8$ seconds were the most predictive of final infarct size ($r^2=0.704$ and $r^2=0.705$, respectively; $P<0.001$; Figures 4 and 5).

**Clinical Severity**

In general, pretreatment perfusion lesion volumes correlated substantially more strongly with pretreatment clinical deficit severity measured on the NIHSS than with day 7 clinical outcome. $T_{\text{max}}$ values $\geq 2$ and $\geq 4$ seconds were most correlated with pretreatment NIHSS ($r=0.753$, $r^2=0.697$, $P<0.0001$), and extent of correlation decreased with increasing perfusion deficit values. $T_{\text{max}} \geq 8$ seconds ($r=0.384$, $r^2=0.200$, $P=0.065$) and $T_{\text{max}} \geq 2$ seconds were most correlative with NIHSS 7 days after treatment. Pretreatment DWI lesion volumes correlated less well with pretreatment NIHSS ($r=0.573$, $P=0.005$) than did pretreatment perfusion volumes. Final infarct volumes correlated with day 7 NIHSS clinical severity ($r=0.478$, $P=0.022$) somewhat more strongly than did the best perfusion threshold volume of $T_{\text{max}} \geq 8$ seconds.

**Discussion**

Our analysis in patients undergoing successful vessel recanalization with intra-arterial thrombolytic therapy uniquely allowed us to identify PWI measures that accurately differentiate irresponsibly injured core from penumbral, salvageable tissue. Using voxel-based analysis, we found that the best threshold for identifying core infarcted tissue is an adjusted $T_{\text{max}}$ of $6$ to $8$ seconds. At this threshold, these measures displayed 53% to 71% sensitivity for identifying infarcted voxels at day 7. In addition, in individual patients, volumes of perfusion deficit at
these thresholds were highly related to the final infarct volumes, as demonstrated by linear regression. Convergent results from the voxel-by-voxel analysis, patient-by-patient PWI volume/final infarct volume analysis, and patient-by-patient PWI volume/day 7 NIHSS clinical deficit analysis indicate robust support for $T_{\text{max}} \geq 6$ to 8 seconds as the most critical threshold differentiating core from penumbral tissues.

Similar to prior studies using other perfusion measurement modalities, we found that early neurological deficits correlated best with likely core plus penumbral lesion volume, represented by modest initial $T_{\text{max}}$ abnormality thresholds, whereas final neurological deficits after recanalization and penumbra salvage correlated best with core lesion volume, represented by more severe initial $T_{\text{max}}$ abnormality thresholds. Similarly, we observed that pretreatment moderate perfusion deficit lesion volumes outperformed pretreatment DWI lesion volumes in correlating with pretreatment clinical severity. Differentiation between true penumbral zones and regions experiencing benign oligemia is a challenge for all perfusion imaging modalities.

Several imaging modalities are available for differentiating core from penumbra, notably PET and single photon emission CT. PET studies suggest that critical absolute thresholds may actually underestimate final infarct size. Low-threshold MR perfusion lesion volumes generated by visual inspection will generally overestimate final infarct size. Our volume-by-volume analysis demonstrates good correlation between pretreatment perfusion volume at $T_{\text{max}} \geq 8$ seconds and final infarct volume. This particular threshold slightly underestimates final infarct volume; however, this compares favorably with earlier comparisons of reduced CBF volumes and final infarcts. Because diffusion-perfusion MRI constitutes an imaging modality that is highly practical in the acute stroke setting, future head-to-head comparisons between MRI-derived CBF, mean transit time (MTT), and $T_{\text{max}}$ volumes are needed to identify accurate predictors of core infarct volumes when making decisions regarding treatment.

Several groups have investigated the role of PWI in identifying penumbra-benign oligemia thresholds. Neumann-Haefelin and colleagues examined untreated patients’ acute perfusion lesions and correlated them with final infarct after lesion growth. They identified time to peak (TTP) delays of $\geq 4$ and $\geq 6$ seconds as being most predictive of lesion enlargement at 6 to 10 days after stroke. A subsequent study showed that TTP $\geq 6$ seconds correlated best with final infarct size ($r=0.73$). Parsons and colleagues identified MTT delays between 4.3 and 6.1 seconds as predicting tissue that evolved to infarction as measured on follow-up MRI between days 30 and 90 in untreated patients. Similarly, Thijs and colleagues identified MTT $> 4$ and $> 6$ seconds as best predicting final infarct size as measured at 4 to 7 days after stroke. All 3 of these studies did not involve thrombolysis or precise knowledge of occurrence or timing of spontaneous vessel recanalization. In addition, these 3 studies compared TTP and MTT values relative to the contralateral MCA territory rather than providing an absolute measure of cerebral perfusion. These studies therefore provide important information regarding differentiation of the ischemic penumbra from benign oligemia, whereas our analysis uniquely differentiates ischemic core from penumbral.

Our findings accord well with these previous observations. It is to be expected that a more severe perfusion threshold will demarcate the core-penumbra border than that which identifies the penumbra-benign oligemia border. The $T_{\text{max}}$ variable we used represents the TTP after deconvolution, and preliminary evidence indicates that $T_{\text{max}}$ values are either equivalent or represent slightly less perfusion deficit for a given time interval compared with TTP and MTT (unpublished data). Therefore, our identification of $T_{\text{max}} \geq 6$ and $\geq 8$ seconds as being most predictive of irreversible infarct despite recanalization and as representing the core-penumbra border is consistent with previous observations.

Our $T_{\text{max}}$ perfusion measure is a novel PWI parameter that measures the TTP of the fraction of tracer present in the voxel or volume of interest at any given time rather than measuring the time that the bolus of contrast takes to traverse the voxel that MTT seeks to quantify. Unlike TTP, $T_{\text{max}}$ is corrected for interindividual variations in extracerebral circulation by deconvolution with an arterial input function, allowing comparisons to be made across individual patients. In addition, MTT requires an assumption of a single, well-mixed compartment; $T_{\text{max}}$ does not. We chose to use $T_{\text{max}}$ rather than MTT for these reasons. Moreover, in prior studies, we have found that $T_{\text{max}}$ has more discriminating value than other candidate indexes that are more dependent on theoretical modeling, such as CBF or cerebral blood volume.

This study allows us the opportunity to take into account the inherent heterogeneity of perfusion in the region of infarct by following voxel fates on an individual basis. Even with these analyses, pretreatment perfusion threshold values performed only modestly well in predicting final tissue infarction. In the voxel-by-voxel analyses, sensitivity and specificity ranged from 50% to 80%, and in the volumetric analyses, pretreatment perfusion volumes accounted for 25% to 29% of the variance in final infarct volume. This modest predictive power likely reflects in part the fact that the pretreatment PWI values indicate the state of perfusion at a single time point and fail to reflect fully greater or lesser degrees of perfusion that have occurred previously. The ACD values, indicating current degree of tissue bioenergetic failure, reflect the cumulative results of prior hypoperfusion over time rather than a single perfusion moment and accordingly provide important additional information regarding tissue fate. Multiparametric analysis of ADC values and perfusion deficit values together, combining information on tissue state and current hemodynamic compromise, would enhance predictions of tissue fate compared with perfusion data alone.

This study has several limitations. The clinical applicability of identifying $T_{\text{max}}$ perfusion thresholds is meaningful only to those treatment centers with the ability to execute the postprocessing involved. With current analysis software, the postprocessing can be completed in 5 to 10 minutes. The small sample size constrained our precision in analyzing the large variation in lesion volumes at varying perfusion thresholds. Although we have identified a discrete level that predicts infarct to a relatively high degree, accuracy may be improved with a larger number of patients or data that allow these patients to be classified in yet another way such as data on tissue state (eg, ADC values). Other PWI-derived indexes of cerebral perfusion such as CBF, cere-
bral blood volume, or MTT might perform better or worse than $T_{\text{max}}$. The relationship between $T_{\text{max}}$ and severity of ischemia may be nonlinear, especially with very low perfusion pressures and vessel collapse. No single perfusion measure has emerged as superior in the MR literature, and $T_{\text{max}}$ has proved most discriminating in our past studies. Imprecise drawing of the border of final infarction may have contributed to suboptimal accuracy of $T_{\text{max}}$, although DWI and FLAIR infarct margins on day 7 scans were generally fairly sharp. Also, because these patients received thrombolysis, volume analysis may not have been as potent as in studies in which thrombolysis was not performed because final lesion volumes in our cohort were frequently quite small. Nonetheless, the convergence between our voxel-by-voxel and volume analyses suggests our findings are robust.

An additional limitation is that our determination of thresholds did not take into account the duration of impaired blood supply. This might be 1 reason that the predictive probability is somewhat low. However, with only 14 patients, the available data set was not extensive enough to allow reliable statistical analysis of time as a factor. In addition, the relatively small range of variation in duration of ischemia intervals among the 14 patients suggests that including time as a factor would have at most only modest effects on the threshold findings.

In conclusion, this study is the first to demonstrate that perfusion thresholds can successfully identify tissue that will evolve to infarction despite early recanalization in human patients, identifying discrete thresholds that accurately differentiate irreversibly infarcted core from ischemic penumbra.

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