Early Diffusion-Weighted Imaging and Perfusion-Weighted Imaging Lesion Volumes Forecast Final Infarct Size in DEFUSE 2

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Background and Purpose—It is hypothesized that early diffusion-weighted imaging (DWI) lesions accurately estimate the size of the irreversibly injured core and thresholded perfusion-weighted imaging (PWI) lesions (time to maximum of tissue residue function [Tmax] >6 seconds) approximate the volume of critically hypoperfused tissue. With incomplete reperfusion, the union of baseline DWI and posttreatment PWI is hypothesized to predict infarct volume.

Methods—This is a substudy of Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study 2 (DEFUSE 2); all patients with technically adequate MRI scans at 3 time points were included. Baseline DWI and early follow-up PWI lesion volumes were determined by the RAPID software program. Final infarct volumes were assessed with 5-day fluid-attenuated inversion recovery and were corrected for edema. Reperfusion was defined on the basis of the reduction in PWI lesion volume between baseline and early follow-up MRI. DWI and PWI volumes were correlated with final infarct volumes.

Results—Seventy-three patients were eligible. Twenty-six patients with >90% reperfusion show a high correlation between early DWI volume and final infarct volume (r=0.95; P<0.001). Nine patients with <10% reperfusion have a high correlation between baseline PWI (Tmax >6 seconds) volume and final infarct volume (r=0.86; P=0.002). Using all 73 patients, the union of baseline DWI and early follow-up PWI is highly correlated with final infarct volume (r=0.94; P<0.001). The median absolute difference between observed and predicted final volumes is 15 mL (interquartile range, 5.5–30.2).

Conclusions—Baseline DWI and early follow-up PWI (Tmax >6 seconds) volumes provide a reasonable approximation of final infarct volume after endovascular therapy. **(*Stroke*. 2013;44:681-685.)**

Key Words: diffusion-weighted imaging ■ irreversible injury ■ ischemic ■ magnetic resonance imaging ■ perfusion-weighted imaging ■ stroke

Early prediction of final infarct volume in ischemic stroke patients is challenging because ischemic lesions evolve over several days in response to numerous variables, including the timing and extent of reperfusion. Severe brain ischemia leads to an intracellular shift of water molecules, which dramatically reduces the normal diffusion of water molecules into and out of cells. Reduced diffusion can be visualized on diffusion-weighted imaging (DWI) scans and quantified on apparent diffusion coefficient maps. For patients who achieve early and complete reperfusion, it has been hypothesized that the DWI lesion volume obtained just before reperfusion can provide an accurate estimate of irreversibly injured tissue that will progress to permanent infarction. However, because increased signal on DWI begins to occur at cerebral blood flow values that are in the penumbral range, DWI lesions are potentially reversible; permanent reversal of DWI lesions has been documented in both experimental models and clinical series. The estimated frequency and volume of DWI reversibility have been controversial with recent large series reporting that this phenomenon is uncommon and typically only involves a small volume of tissue.[1–3] Data from the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study suggest that using an apparent diffusion coefficient threshold of ≈600 can limit the degree of DWI reversibility.[4]

Perfusion-weighted imaging (PWI) identifies hypoperfused tissue and has the potential to identify tissue that is likely to progress to infarction if timely reperfusion does not occur. An essential issue related to PWI is that an appropriate threshold must be applied to exclude ischemic tissue that is unlikely to become permanently injured even if reperfusion does not occur (ie, benign oligemia). Recent studies, including DEFUSE and Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET), have used time to maximum

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of tissue residue function (Tmax) as the perfusion parameter of choice and found that a Tmax contrast arrival delay of >4 to 6 seconds optimally predicts ischemic tissue destined to become infarcted in patients who did not achieve reperfusion.[5] Furthermore, a Tmax threshold in the range of 5 to 6 seconds has been shown to correspond well with penumbral cerebral blood flow values on positron emission tomography[6] and Xenon CT.[5]

The accuracy of DWI and PWI for the prediction of final infarct volume has not been well established. Multiple different definitions of nonviable versus penumbral tissue have been proposed and most thresholds have not been prospectively evaluated.[7] On the basis of post hoc analyses of DEFUSE and EPITHET, the DEFUSE 2 trial chose an apparent diffusion coefficient threshold of <600 as the optimal DWI threshold for the identification of ischemic core and a Tmax >6 seconds threshold for the identification of tissue that is likely to progress to infarction if early reperfusion does not occur. We performed a prospective assessment of these prespecified DWI and PWI thresholds to determine the accuracy of early DWI and PWI lesions for predicting infarct volume. We hypothesized that the baseline DWI lesion would predict the size of the 5-day infarct in patients who experience complete reperfusion as documented on the follow-up PWI scan. We also predicted that the tissue which had Tmax delays >6 seconds on the baseline scan would go on to infarction if reperfusion did not occur. Furthermore, we hypothesized that the combination of the baseline DWI and the brain regions that remained PWI positive on the follow-up MRI would predict the 5-day infarct volume.

DEFUSE 2 represents a unique opportunity to examine the role of DWI and PWI to predict infarct volume because patients had an MRI performed just before, and shortly after, endovascular therapy. This provided a group of patients who had different degrees of reperfusion.

Methods

The methodology and main results of DEFUSE 2 have been published.[8] In this National Institutes of Health-sponsored multicenter prospective cohort study, MRI scans were obtained before endovascular stroke therapy (femoral puncture within 12 hours of onset of symptoms). An MRI was repeated within 12 hours after completion of the procedure and again at 5 days after onset. For inclusion in this substudy, subjects were required to have technically adequate MRI scans at all 3 time points.

Initial baseline and early follow-up PWI images were generated using the RAPID software.[9] When needed, the DEFUSE 2 core laboratory corrected the automated the volume assessments to adjust for overestimation or underestimation of the lesion volume, using the software Medical Image Processing, Analysis, and Visualization (MIPAV).[10] Five-day fluid-attenuated inversion recovery volumes were outlined and subsequently corrected for edema using a validated technique.[11] The edema-corrected 5-day fluid-attenuated inversion recovery was defined as the final infarct volume. The initial DWI scan was coregistered with the early follow-up PWI (Tmax >6 seconds) scan, creating the union of the 2 volumes.

Reperfusion was defined on the basis of the reduction in PWI lesion volume between baseline and early follow-up MRI. Percentage reperfusion was calculated by taking the difference between baseline PWI (Tmax >6 seconds) and early follow-up PWI (Tmax >6 seconds) volumes and dividing it by the baseline PWI (Tmax >6 seconds) volume. Patients were then separated into a complete reperfusion group (>90%) and a no reperfusion group (<10%). Patients with 90% to 100% reperfusion were defined as having complete reperfusion, and for these patients, the initial DWI volume was compared with the final infarct volume. Patients with <10% reperfusion were considered to have no reperfusion, and for these patients, the final infarct volume was compared with the baseline PWI lesion. For all patients, the union of baseline DWI with early follow-up PWI was compared with the final infarct volume.

Linear regression analysis was used to assess the relationship between predictor volumes and final infarct volumes. In particular, regression line slopes (using no-intercept regression) and correlation coefficients were estimated. We used robust regression with least trimmed squares estimation to account for outliers.[12] In addition, the median values were calculated for the difference between predicted final volumes and actual final volumes. Because an individual patient could have a final lesion volume that was larger or smaller than the predicted volume, the absolute value of the difference was also used to generate the median of the absolute value of the difference between predicted and observed volumes.

In addition to calculating a slope and correlation coefficient for all 3 analyses described before, a Bland-Altman analysis of agreement[13] was created to examine if the discrepancy between the predictor volume (union of DWI and PWI) and the final infarct volume consistently varied toward overestimation or underestimation. Also, this allowed for the analysis of the percentage of patients with an actual final infarct volume within 25 mL or 35 mL of the predicted volume.

Results

One hundred and ten patients were in the endovascular cohort of DEFUSE 2, and of these, 104 had a technically adequate baseline DWI and PWI. Five of these patients were excluded from the analysis because reperfusion could not be assessed due to baseline PWI lesions < 10 mL. In addition, 5 did not have an early follow-up scan, 16 did not have a 5-day MRI, and 5 had >18 hours between catheterization and early follow-up MRI scan. Therefore, 73 patients were eligible for this analysis. The timing of the MRI scans and the baseline characteristics of the patients are summarized in the Table. The core laboratory made adjustments in the DWI lesion volume of 4 patients.

Twenty-seven patients had >90% reperfusion. The regression line between baseline DWI lesion and final infarct volumes (see Figure 1) in these patients had a slope of 1.78 (r=0.95; $P < 0.001$) using robust regression. The median of the absolute values of the difference between the baseline DWI volume and the final infarct volume was 8.3 mL (interquartile range [IQR], 2.4–45.0), and the median difference between baseline DWI volume and final volume was 5.62 (IQR, 0.9–39.9). Only 2 patients had final infarct volumes that were >2 mL smaller than the baseline DWI. Nine patients had <10% reperfusion. The regression line between baseline PWI (Tmax >6 seconds) volume and final infarct volume (see Figure 2) had a slope of 1.35 (r=0.86; P=0.002). Among all 73 patients, the union of the coregistered baseline DWI with early follow-up PWI lesions was highly correlated with final volume with a slope of 0.97 (r=0.94; P<0.001) (see Figure 3) using robust regression. The median of the absolute values of the differences between observed and predicted final volumes was 15 mL (IQR, 4.8–32.8), and the median difference between predicted and actual final infarct volumes was −0.1 mL (IQR, −19.8 to 12.5) (see Figure 4). Sixty-seven percent of patients had a predicted volume that fell within 25 mL of their actual final infarct volume, and 79% were within 35 mL of their actual final lesion volume.

Table. Baseline Characteristics, Endovascular Therapies Used, and Time Between Scans for Patients Analyzed

Characteristics	
Age, mean (SD)	62 (16)
Male sex, n (%)	38 (52)
White ethnicity, n (%)	64 (88)
Comorbidities, n (%)	
Previous MI	7 (11)
Hypertension	46 (66)
Atrial fibrillation	25 (36)
Diabetes mellitus	15 (21)
Hyperlipidemia	35 (49)
Volumes, median (IQR), mL	
Baseline DWI	16.0 (8.0–32.8)
Baseline PWI	81.0 (58.4–117.0)
Early follow-up PWI	19.3 (3.1–50.8)
Five-day FLAIR (uncorrected)	74.7 (25.1–137.6)
Five-day FLAIR (corrected)	48.4 (21.6–81.7)
Devices used, n (%)	
IV tPA pretreatment	38 (52)
Merci device	36 (49)
Penumbra system	35 (48)
Intra-arterial tPA	32 (44)
Others	18 (25)
Time, median (IQR), h	
Onset to MRI	4.6 (2.7–6.8)
Onset to femoral puncture	6.0 (3.8–8.3)
Baseline MRI to early follow-up MRI	3.7 (2.0–6.6)
Onset to FLAIR	119.7 (97.2–131.1)

DWI indicates diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; IV, intravenous; MI, myocardial infarction; PWI, perfusion-weighted imaging; and tPA, tissue plasminogen activator.

Discussion

Identification of salvageable tissue remains an important consideration in the treatment of acute stroke, and identification of patients who are likely to have continued infarct growth may have therapeutic implications.[8] The key finding of this prespecified analysis of DEFUSE 2 is that early DWI and PWI volumes are predictive of final infarct volume.

Early DWI volume appears to provide a reasonable surrogate of irreversibly injured lesion core; patients who had complete reperfusion had final lesion volumes that were highly correlated to the baseline DWI volume. Final infarct volumes were virtually never smaller than the baseline DWI, suggesting that permanent DWI reversal is minimal after endovascular reperfusion. Final infarct volume was typically about 5mL larger than the baseline DWI which could be a result of continued growth of the DWI lesion between the time of MRI and the time of reperfusion. The median time from MRI to femoral puncture was 0.7 hours (IQR, 0.6–1.0), and the median time from the start of the MRI to the completion of the procedure was 1.5 hours (IQR, 1.1–2.2).

PWI (Tmax >6 seconds) provides a reasonable surrogate for critically hypoperfused tissue that will likely die without successful reperfusion. In patients who did not achieve reperfusion, baseline PWI was highly correlated with final infarct volume. However, the sample size for this analysis was very small owing to the low rate of no reperfusion in DEFUSE 2.

More complete data regarding the accuracy of PWI (Tmax >6 seconds) for the identification of tissue that is likely to go on to infarction are provided by the analysis of the union of baseline DWI and early follow-up PWI for the prediction of final infarct volume (n=73). Our hypothesis was that the baseline DWI represents the ischemic core and the follow-up PWI represents the tissue that was not salvaged by reperfusion; thus, the union of these 2 volumes should predict the final infarct. We found a strong correlation with a slope of 1. A slope significantly >1 would indicate that the PWI volume is likely to underestimate critical hypoperfusion whereas a slope <1 would suggest underestimation. Overestimation of critical hypoperfusion has been a common limitation of PWI[5] and is the reason why a more stringent Tmax threshold (>6 seconds) was chosen for DEFUSE 2. These data provide prospective validation that Tmax >6 seconds does not consistently over- or underestimate the region of critically hypoperfused tissue.

The overall accuracy for predicting final infarct volume was reasonable; the median absolute difference between predicated

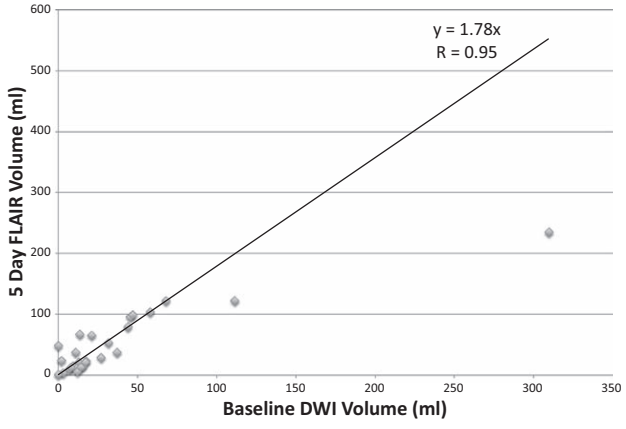

Figure 1. Correlation of baseline diffusion-weighted imaging (DWI) volume to final infarct fluid-attenuated inversion recovery (FLAIR) volume in patients with >90% reperfusion.

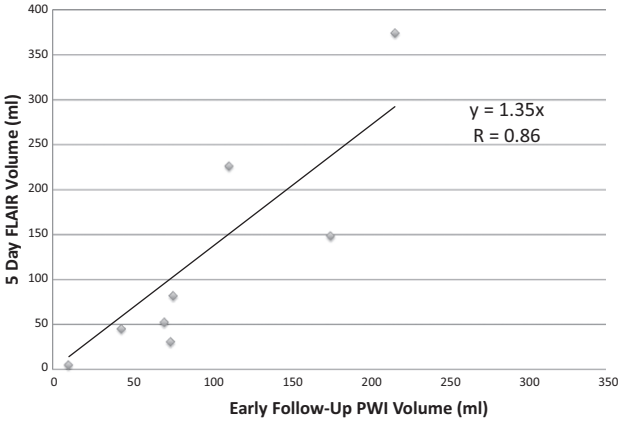

Figure 2. Correlation of early follow-up perfusion-weighted imaging (PWI) volume to final infarct fluid-attenuated inversion recovery (FLAIR) volume in patients with <10% reperfusion.

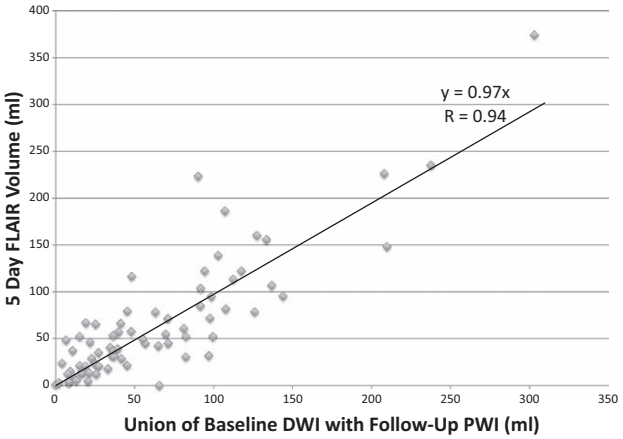

Figure 3. Correlation of union of baseline diffusion-weighted imaging (DWI) with early follow-up perfusion-weighted imaging (PWI) volume to final infarct fluid-attenuated inversion recovery (FLAIR) volume in patients with partial reperfusion.

and actual infarct volumes was 15 mL. Brain ischemia is a dynamic process, which may be influenced by numerous unforeseen events such as hemodynamic factors, metabolic changes, and ongoing thromboembolism and hemorrhage. Therefore, it is not unexpected that imaging assessments at 1 or 2 early time points are not able to precisely predict infarct volume in all patients.

This study has several limitations. Multiple techniques for endovascular therapy were used in this study; this additional variable could have affected the time between baseline MRI and revascularization and the degree of reperfusion obtained. The time between the onset of symptoms and the baseline and follow-up MRI was also variable. Final infarct volume was estimated from MRI scans obtained 5 days after the onset of symptoms. Automated DWI and PWI volumes required manual correction in some cases.

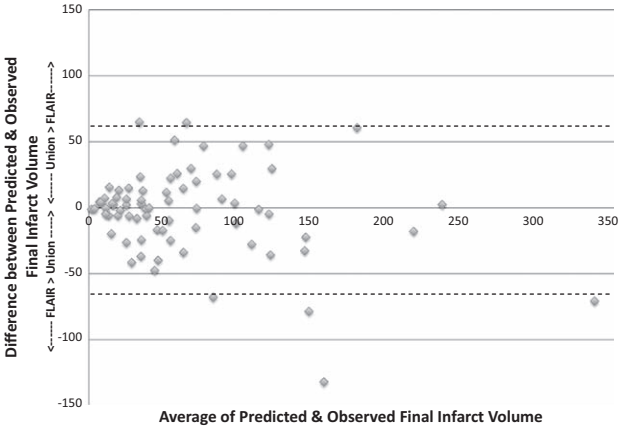

Figure 4. Bland-Altman analysis of agreement with 95% limits of agreement. Predicted final infarct volume is the union of the baseline diffusion-weighted imaging and the follow-up perfusion-weighted imaging volumes. Observed final infarct volume is the corrected 5-day fluid-attenuated inversion recovery (FLAIR) volume. Patients with a positive difference have a predicted volume that is greater than the observed volume; patients with a negative difference have a predicted volume that is less than the observed volume.

These results have implications for future clinical trials. Because permanent reversal of early DWI lesions (even following complete reperfusion) appears to be very rare, DWI reversal does not appear to be a realistic end point for clinical trials. The fact that the Tmax threshold of >6 seconds neither consistently over- or underestimated infarct volume suggests that this threshold is appropriate for use in future trials. However, because the Tmax >6 volume did not accurately predict infarct volume in several individual patients, further efforts to identify additional factors that can improve the prediction of infarct volume should be explored. For example, parameters that may reflect the degree of collateral circulation, such as cerebral blood volume measurements, are currently being explored in the DEFUSE 2 data set.

In summary, the union of the early DWI (apparent diffusion coefficient <600) and follow-up PWI (Tmax >6 seconds) volumes provides a reasonable approximation of final infarct volume after endovascular therapy. Automated DWI and PWI volumes can be useful for predicting which acute stroke patients are most likely to have continued infarct growth.

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Disclosures

Dr Albers has equity interest in iSchemaView and has worked as a consultant for Covidien and Stryker. Dr Bammer has equity interest in iSchemaView. Dr Zaharchuk receives modest research funding support from GE Healthcare. The other authors have no conflicts to report.

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