Geography, Structure, and Evolution of Diffusion and Perfusion Lesions in Diffusion and Perfusion Imaging Evaluation For Understanding Stroke Evolution (DEFUSE)

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Background and Purpose—The classical representation of acute ischemic lesions on MRI is a central diffusion-weighted imaging (DWI) lesion embedded in a perfusion-weighted imaging (PWI) lesion. We investigated spatial relationships between final infarcts and early DWI/PWI lesions before and after intravenous thrombolysis in the Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study.

Methods—Baseline and follow-up DWI and PWI lesions and 30-day fluid-attenuated inversion recovery scans of 32 patients were coregistered. Lesion geography was defined by the proportion of the DWI lesion superimposed by a $T_{\text{max}}$ lesion; Type 1: $>50\%$ overlap and Type 2: $\leq50\%$ overlap. Three-dimensional structure was dichotomized into a single lesion (one DWI and one PWI lesion) versus multiple lesions. Lesion reversal was defined by the percentage of the baseline DWI or PWI lesion not superimposed by the early follow-up DWI or PWI lesion. Final infarct prediction was estimated by the proportion of the final infarct superimposed on the union of the DWI and PWI lesions.

Results—Single lesion structure with Type 1 geography was present in only 9 patients (28%) at baseline and 4 (12%) on early follow-up. In these patients, PWI and DWI lesions were more likely to correspond with the final infarcts. DWI reversal was greater among patients with Type 2 geography at baseline. Patients with multiple lesions and Type 2 geography at early follow-up were more likely to have early reperfusion.

Conclusion—Before thrombolytic therapy in the 3- to 6-hour time window, Type 2 geography is predominant and is associated with DWI reversal. After thrombolysis, both Type 2 geography and multiple lesion structure are associated with reperfusion. *(Stroke. 2009;40:00-00.)*

Key Words: brain infarction ■ magnetic resonance ■ thrombolysis

Multimodal MRI is a technique of choice to assess patients with acute ischemic stroke.\(^1\) Diffusion-weighted imaging (DWI) demonstrates the presence of cytotoxic ischemic injury within minutes and provides an estimate of the volume of the final infarct in patients who do not experience early reperfusion.\(^2\) Perfusion-weighted imaging (PWI) provides an assessment of cerebral hemodynamics. The PWI/DWI mismatch hypothesis postulates that the difference between the acute PWI and DWI lesions provides an estimate of the ischemic penumbra. The Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) and the Echoplanar Imaging THrombolytic Evaluation Trial studies demonstrated strong associations among recanalization, reperfusion, reduced infarct growth, and favorable clinical response in patients with a PWI/DWI mismatch treated with intravenous tissue plasminogen activator (tPA) within 3 to 6 hours of symptom onset.\(^3\)–\(^5\) In these studies, mismatch was defined by a PWI lesion volume (determined by a $T_{\text{max}} >2$-second delay) that was at least 20% larger than the acute DWI lesion volume.

Based on the mismatch hypothesis, an ischemic lesion composed by a central core (DWI lesion) embedded in a penumbra (DWI/PWI mismatch) has become the classical representation of acute ischemic stroke geography.\(^6\)–\(^7\) However, several studies have contested the universality of this representation. First, it has been demonstrated that PWI
lesions defined by $T_{\text{max}} > 2$-second delay overestimate the volume of critically hypoperfused tissue defined by positron emission tomography scan or Xenon CT, and using PWI thresholds such as a Tmax threshold of $> 4$ to 6 seconds appears to provide a more accurate estimation of penumbral tissue. Second, early recanalization is associated with reversal of acute DWI lesions; however the use of apparent diffusion coefficient thresholds may help separate reversible from irreversible DWI lesions. Third, coregistration of acute DWI lesions with contemporaneous positron emission tomography scan imaging demonstrates that DWI lesions have a heterogeneous structure and include regions of variable metabolic disruption and perfusion. Finally, coregistration of acute DWI/PWI lesions has shown that the most of the reversible part of the acute DWI lesion is not superimposed by a PWI lesion defined by $T_{\text{max}} > 2$ seconds. Altogether, these findings emphasize the heterogeneity and complexity of the acute PWI and DWI lesions that define the anatomy of the MRI penumbra. Coregistration of sequential MRI images allows visualization of the spatial relationships between PWI and DWI lesions at different time points as well as the evolution of individual lesions between time points. Three-dimensional analyses allow visualization of the structure of individual lesions.

To help clarify the natural history, topography and structure of PWI and DWI lesions during the first hours of acute ischemic stroke as well as their impact on prognosis and final infarct volume and location, we used the DEFUSE data set to examine spatial relationships between early DWI and PWI lesions and their associations with final infarct volume and location. We hypothesized that the classical single centripetal geography of the ischemic core and penumbra would evolve during the early hours after stroke onset and administration of thrombolytic therapy. Furthermore, we hypothesized that this evolution would influence the accuracy of predicting the location of the final infarct.

**Methods**

The inclusion criteria, MRI protocol, study design, and primary results of the DEFUSE trial have been previously reported. In brief, patients were treated with intravenous tPA 3 to 6 hours after stroke onset and MRI scans were obtained just before tPA therapy, 3 to 6 hours after tPA, and at 30 days. For this substudy, the baseline and early follow-up DWI and PWI scans as well the 30-day fluid-attenuated inversion recovery scans were coregistered using SPM5. The inclusion criteria, MRI protocol, study design, and primary results of the DEFUSE trial have been previously reported. In brief, patients were treated with intravenous tPA 3 to 6 hours after stroke onset and MRI scans were obtained just before tPA therapy, 3 to 6 hours after tPA, and at 30 days. For this substudy, the baseline and early follow-up DWI and PWI scans as well the 30-day fluid-attenuated inversion recovery scans were coregistered using SPM5.

**Study Plan**

Inclusion criteria consisted of (1) a technically adequate baseline DWI and PWI; and (2) a measurable baseline DWI lesion and a baseline PWI lesion (defined by $T_{\text{max}} > 4$ seconds) $> 10$ mL (Figure 1).

**Definitions**

The geography of the mismatch was investigated by determining the proportion of DWI lesion superimposed by a $T_{\text{max}} > 4$ seconds PWI lesion. We dichotomized into 2 groups: Type 1 geography was defined when $> 50\%$ of DWI lesion volume superimposed with a PWI value of $T_{\text{max}} > 4$ seconds. Type 2 geography was defined as the remaining patients ($\leq 50\%$ of the DWI lesion volume superimposed with $T_{\text{max}} > 4$ seconds) (Figure 2A).

The structure of baseline DWI and PWI lesions was assessed using 3D-Doctor Software (Able Software Corp, Lexington, Mass). We classified the three-dimensional structure into 2 subtypes: (1) single DWI and PWI lesion; and 2) multiple DWI and/or PWI lesions separated by at least 5 mm with the smaller lesion larger than 10% of the total lesion volume (1) or more than 10 distinct fragments separated by at least 5 mm regardless of size (2) (Figure 3A). Thus, the “classical” penumbral mismatch pattern was considered to have both Type 1 lesion geography and a single structure.

Early DWI reversal was defined by the percentage of the acute DWI lesion with no superimposed DWI lesion on the early (3 to 6 hours) follow-up study. Early DWI extension was defined as the percentage of the baseline DWI lesion that extended beyond its initial location on the early follow-up study. The same definitions were applied to PWI lesions.
A favorable clinical response was defined as a National Institutes of Health Stroke Scale (NIHSS) score of 0 to 1 or 8 points of improvement between baseline and 30 days.

We investigated the percent of the final infarct on 30-day fluid-attenuated inversion recovery that was predicted by the union of DWI and PWI lesions at baseline and follow-up time points. This rate was determined by the percentage of the volume of the final infarct that was superimposed on the coregistered DWI and PWI lesions at each time point.

Statistical Analysis

The Mann–Whitney U test was used to compare groups defined by favorable clinical response, lesion structure, and geography. The Wilcoxon signed rank test was used to compare baseline and follow-up values. We used the chi² test to compare proportions, t test to compare means, and the McNemar test to compare the evolution of lesion type and structure over time. The correlation between DWI and PWI evolution was estimated using Spearman correlation coefficient. An overall significance level was maintained at P < 0.05.

Group descriptive values are reported as median (interquartile range) unless explicitly referred as mean ± SE.

Results

Baseline Characteristics and Mismatch Geography

Thirty-two patients met the inclusion criteria (Figure 1). Their mean ± SE age was 69 ± 3 years old and the baseline NIHSS was 13 (range, 9 to 16).

On baseline MRI, 12 (38%) of the patients had a Type 1 geography (ie, DWI/PWI overlap > 50%) with an overlap rate of 59% (range, 55 to 63) and 20 (62%) had Type 2 (ie, DWI/PWI overlap ≤ 50%) with an overlap rate of 25% (range, 15 to 37; Figure 2A). Compared with the patients with Type 2 baseline geography, baseline Type 1 geography was associated with a larger median baseline DWI lesion volume, larger median baseline PWI lesion size, and larger final infarct volume on 30-day fluid-attenuated inversion recovery. There was no difference in mean age, median baseline National Institutes of Health Stroke Scale, time to MRI, or time to treatment between the 2 groups (Table).

The follow-up MRI was obtained after a median delay of 5.5 hours (range, 4.6 to 6.6 hours) after tPA therapy after baseline scan. The majority of the patients (75%) with Type 1 geography at baseline had Type 2 geography at first follow-up. In addition, virtually all of the patients (19 of 20) with baseline Type 2 geography maintained this pattern at follow-up (P = 0.021; Figure 2B). The one exception was a patient with 49% overlap at baseline and 51% overlap at first follow-up. Therefore, at first follow-up, nearly 90% of the patients had Type 2 geography and a DWI/PWI overlap rate of only 13% (range, 6% to 34%). The remaining 4 patients with Type 1 geography had an overlap rate of 60% (range, 52% to 69%).

Three-Dimensional Structure

Baseline DWI lesions were single in 26 (81%) patients and multiple in 6 (19%). Baseline PWI lesions were single in 23 (72%) patients and multiple in 9 (28%); (Table; Figure 3A).

Both DWI and PWI were single lesions at baseline in 20 patients (63%). Nine patients (75%) with Type 1 geography versus 11 (55%) patients with Type 2 geography had a single lesion structure for both PWI and DWI (P = 0.045). Overall, 9
patients (28%) had the classical mismatch pattern at baseline with both a single lesion structure and Type 1 geography. Early follow-up DWI lesion structure analysis demonstrated 28 (87.5%) single lesions; 4 (12.5%) patients had multiple DWI lesions. Follow-up PWI lesion analysis demonstrated 20 (62%) patients with single lesions and 12 (38%) with multiple lesions. Both the DWI and PWI structure was a single lesion at early follow-up in 19 patients (59%). All 4 patients with multiple PWI lesions, the mean T_max value was 17 seconds (±39 SE). Seventy-two percent of these regions had a T_max delay >8 seconds.

**DWI and PWI Evolution**

**DWI/PWI Relationships**
Fifty-three percent of the baseline DWI lesion volume was not superimposed with a PWI lesion (defined by T_max >4 seconds). The mean T_max value within these regions was 0.7 seconds (±0.005 SE). Eleven percent of these regions had a T_max delay >2 seconds and ≤4 seconds. For the regions of the DWI lesions that were superimposed with PWI lesions, the mean T_max value was 17 seconds (±39 SE). Seventy-two percent of these regions had a T_max delay >8 seconds.

**DWI Lesion Evolution**

Coregistration revealed that 39% (range, 23 to 52) of the baseline DWI volume was not superimposed on the first follow-up DWI. However, the follow-up DWI lesion typically involved additional regions that were not DWI-positive at baseline. The volume of these “new” DWI regions was 56% (range, 29 to 80) of the baseline DWI lesion. Because of these new areas of diffusion positivity, the early follow-up DWI volume of 17 mL (range, 7 to 32 mL) was larger than the baseline DWI lesion of 13 mL (range, 7 to 35 mL; P=0.014).

Early DWI reversal was higher among patients who had baseline Type 2 geography; 46% (range, 33% to 61%) compared with Type 1 geography: 23% (range, 16% to 42%; P=0.048; Figure 4A). DWI reversal also tended to be higher among patients Type 2 versus Type 1 geography at the time of early follow-up: 44% (range, 25% to 58%) versus 24% (range, 12% to 33%; P=0.074). Early DWI extension was not associated with either baseline or follow-up geography.

Neither early DWI reversal nor extension was associated with baseline DWI or PWI three-dimensional structure.

**PWI Lesion Evolution**

Seventy-four percent (range, 42% to 92%) of the baseline PWI lesion was reversed, whereas new regions of PWI abnormality were also noted. These “new regions” of PWI abnormality seen on the early follow-up scans typically had a volume of approximately 25% (range, 8% to 59%) of the baseline PWI lesion. The early follow-up PWI lesion volume of 12.4 mL (range, 4 to 54 mL) was smaller than the baseline volume of 42.6 mL (range, 18 to 65 mL; P=0.003). There was a moderate correlation (R=0.558; P=0.001) between DWI and PWI reversal; however, no correlation was found between DWI and PWI extension (R=−0.179; P=0.33).

PW1 reversal was higher (78% [range, 53% to 92%]) among patients with Type 2 geography at the time of the early follow-up scan compared with those with Type 1 geography at early follow-up (34% [range, 21% to 43%]; P=0.011; Figure 4C). PWI extension was not associated with either baseline or follow-up geography.

PW1 reversal was higher among patients with multiple lesion structure (DWI or PWI) at the time of early follow-up, 91% (range, 74% to 95%) versus 47% (range, 33% to 78%; P=0.003; Figure 4D). PWI lesion extension was less in
patients who had a single baseline PWI lesion, 19% (range, 6% to 39%) versus 67% (range, 37% to 185%; \( P = 0.024 \)).

Clinical Outcome and DWI/PWI Lesion Evolution, Structure, and Geography
Fifteen patients (47%) experienced a favorable clinical response, whereas 17 (53%) did not. The occurrence of favorable clinical response was not associated with the evolution (reversal, extension) or the structure of baseline PWI or DWI lesions. Six patients (50%) with baseline Type 1 geography and 9 (45%) with baseline Type 2 geography had a favorable clinical response (\( P = 1 \)).

Final Infarct Prediction From the Union of PWI and DWI
Fifty-seven percent (range, 45% to 69%) of the final fluid-attenuated inversion recovery lesion was superimposed on the union of DWI and PWI lesions from the baseline MRI. This rate was increased among patients with a baseline Type 1 geography compared with patients with Type 2: 68% (range, 60% to 74%) versus 53% (range, 37% to 63%; \( P = 0.009 \)). Patients with a single DWI and PWI lesion at baseline had a larger proportion of final infarct superimposed on the union of the baseline DWI and PWI lesions: 65% (range, 54% to 74%) versus 44% (range, 30% to 56%; \( P = 0.001 \)).

Sixty-one percent (range, 35% to 72%) of the final infarct was superimposed on the union of DWI and PWI lesions from the early follow-up MRI. Lesion geography on the early follow-up MRI was not associated with final infarct prediction. Patients with the single lesion structure at follow-up had a larger proportion of the final infarct superimposed on the union of the follow-up DWI and PWI lesions: 64% (range, 58% to 75%) versus 51% (range, 20% to 61%; \( P = 0.024 \)).
Discussion

Our study illustrates the evolution of acute DWI and PWI lesions in patients with acute stroke using objective measurements of the lesion size and location in coregistered images obtained before and after tPA administration. Our key findings are that the classical representation of the early ischemic lesion, an area of restricted diffusion embedded in a critical PWI lesion (i.e., Type 1 geography with a single lesion structure), is present in only approximately 30% of patients who are imaged 3 to 6 hours after symptom onset. In addition, there are substantial fluctuations in volume, location, and structure of DWI and PWI lesions during the early hours after stroke onset. Furthermore, spatial relationships between DWI and PWI lesions are associated with the probability that a lesion will evolve into final infarction.

Evolution of PWI and DWI Lesions

As expected, our patients demonstrated a significant reduction of the pretreatment PWI volume 3 to 6 hours after tPA therapy. This reduction involved substantial PWI lesion reversal combined with modest extension into regions of normal PWI at baseline.

DWI lesions also demonstrated both regression as well as extension in the early hours after tPA administration. We have previously demonstrated that absence of recanalization and increased severity of the superimposed PWI lesion (based on T_max delay) are associated with DWI evolution to final infarction.14 Compatible with these findings, the present study demonstrates that baseline Type 2 geography (>50% of DWI with no superimposed PWI) and PWI reversal both favored early DWI lesion reversal.

Recently, we introduced the term RADAR (Reversible Acute Diffusion lesion Already Reperfused) to describe regions of acute restricted diffusion with no superimposed PWI lesion defined by T_max delays.14 In the DEFUSE data set, these regions are associated with high rates of DWI reversal. In addition, DWI reversal in these regions is associated with favorable clinical outcomes. These findings imply that the RADAR regions comprise an important sector of the ischemic penumbra. The Type 2 geography pattern was based on our prior observations that RADAR accounts for a substantial percentage of the acute DWI lesion and this pattern differs from the classical single centripetal representation of the ischemic core and penumbra. In addition, the classical concept of the origin of a typical stroke is a single region of hypoperfusion, rather than multiple separate lesions, DWI and PWI structure (single versus multiple lesions) was independently assessed.

We found that a single DWI and PWI lesion at baseline was more common than multiple lesions; however, the spatial relationships of the lesions typically differed from the classical concept (Figure 1). The 2 approaches used to define structure and geography shared some common findings: both Type 1 geography and single lesion structure were associated with larger baseline DWI and PWI lesion volumes. Their counterparts, Type 2 geography and multiple lesion structure, were both associated with reperfusion. We suspect that the presence of Type 2 geography before thrombolysis reflects spontaneous migration and/or fragmentation of acute thromboli. Geography and structure differed in several important ways. For example, approximately half (11 of 20) of the patients with the single lesion pattern at baseline had Type 2 geography. In addition, progression from Type 1 to Type 2 geography on the early follow-up scan occurred in two thirds of the patients, whereas less than one third of the patients who had single lesions at baseline evolved to the multiple lesion structure at early follow-up. These findings suggest that after tPA therapy, reperfusion of the acute DWI lesion typically occurs without significant fragmentation of the ischemic lesions.

Persistence of Type 1 geography and single lesion structure were both predictors that the final infarction would be substantially superimposed on the baseline PWI and DWI lesions. Several algorithms/prediction models have been proposed using both DWI and PWI values to predict the final infarct from acute DWI and PWI data.15,16 Our findings suggest that an assessment of lesion geography and structure may improve the predictive accuracy of these models.

Study Limitations

The primary limitation of our study is a small sample size. Many of the DEFUSE patients were excluded because of small or absent baseline lesions. In addition, some of the patients with the most severe strokes did not return for the 30 day follow-up MRI. This limitation might contribute to the lack of relationship among structure, geography, and clinical outcomes. This lack of association is intriguing because both Type 1 geography and single lesion structure were associated with larger baseline DWI and PWI lesions and Type 1 geography was associated with larger final infarct volumes. In addition, our results apply only to the DEFUSE time window (imaging studies performed from 4.5 to 10 hours after symptom onset) in patients who were all treated with tPA after the initial MRI. Future analyses, focused on earlier time points and untreated patients, are needed to determine the natural history and clarify any impact of our findings on management of patients with acute stroke. Further analyses focusing on clinical outcomes with larger data sets are currently in progress.

Type 2 geography was defined on the basis of a T_max threshold >4 seconds. We acknowledge that T_max is only a surrogate of cerebral blood flow that does not directly reflect cerebral blood flow. DWI map generation was based on signal intensity on the b1000 map and did not directly take into account apparent diffusion coefficient thresholds that may provide a more accurate prediction of infarct core. Future analyses using apparent diffusion coefficient thresholds are also ongoing.12

Conclusions

In untreated patients imaged with MRI 3 to 6 hours after symptom onset, only approximately 30% demonstrate the classical concept of a central area of restricted diffusion surrounded by a hypoperfused penumbra. One third of the patients had multiple discrete regions of restricted diffusion or perfusion and in more than two thirds, the majority of the DWI lesion did not have a superimposed perfusion lesion. This pattern (Type 2 geography) was associated with a high...
rate of acute DWI reversal. After tPA therapy, Type 2 geography and multiple lesion structure were associated with a high rate of reperfusion. After thrombolysis, virtually all patients displayed Type 2 geography, whereas most maintained a single lesion structure. In addition, spatial relationships between DWI and PWI lesions were associated with the percentage of the final infarct volume that could be predicted based on the size and location of the baseline DWI and PWI lesions.

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Disclosures
None.

References

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