Is White Matter More Prone to Diffusion Lesion Reversal After Thrombolysis?

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Background and Purpose—In acute ischemic stroke, white matter (WM) is considered more resistant to infarction than gray matter (GM). To test this hypothesis, we compared the fate of WM and GM voxels belonging to the acute diffusion-weighted imaging (DWI) lesion, expecting WM voxels to be more prone to reversal after thrombolysis.

Methods—Reversible acute DWI (RAD) lesion was defined voxel-wise as an acute lesion on initial DWI (DWI1) with no visible lesion on 24-hour DWI (DWI2). Only patients with RAD lesions >10 mL and >10% of DWI1, from our previously reported cohort were eligible. The core was defined as voxels hyperintense on DWI1 and DWI2, semi-automated segmentation of DWI1, core, and RAD lesions, normalization into standard space, and WM/GM segmentation allowed calculations of WM/GM proportions in each region of interest using a voxel-counting algorithm.

Results—Thirty patients were eligible (RAD lesion median volume [interquartile range], 23.3 mL [19.1–35.0 mL]; onset-to-treatment time, 134 minutes [105–185 minutes]). WM voxels fraction was greater in RAD lesions than in the core (59.4% [52.8%–68.9%] versus 49.6% [43.0%–57.5%]; P=0.011). The proportion of reversibility was greater for WM than for GM voxels (60.8% [25.5%–88.7%] versus 53.5% [21.1%–77.3%]; P=0.02). The percentage of RAD lesions increased with the proportion of WM present in the acute DWI lesion (P<0.0001; R=0.67).

Conclusions—Acute DWI lesions predominantly involving WM may be more prone to reversal and, hence, to respond to therapy than their GM counterparts. (Stroke. 2014;45:1167-1169.)

Key Words: diffusion magnetic resonance imaging ■ ischemia ■ magnetic resonance imaging ■ stroke ■ thrombolytic therapy

Given their markedly different cellular constituency, vascular anatomy, and metabolic rate, gray matter (GM) and white matter (WM) may have differential vulnerability to acute ischemia. Accordingly, animal and human studies based on histopathology or imaging have suggested that WM is more resistant than GM. Assessing the fate of GM versus WM within the acute diffusion-weighted imaging (DWI) lesion may serve to test this hypothesis. Whether WM lesions are more prone to reversal than GM lesions is also clinically relevant because if true, it would imply that reperfusion would be more efficient if DWI lesions predominate in WM. Supporting this hypothesis, our personal experience and observations by others suggest that reversible acute DWI (RAD) lesions predominate in WM. However, these reports are based on visual inspection rather than quantitative analysis. Here, we compared the fate of WM and GM voxels belonging to the acute DWI lesion by assessing their reversibility at follow-up imaging.

Patients and Methods

In our previously reported sample of 176 consecutive patients with thrombosis ≤4.5 hours from onset, RAD lesion was mapped voxel-wise as the acute lesion on pretreatment DWI (DWI1) not visible on the coregistered 24-hour follow-up DWI (DWI2). For the present study, to avoid segmentation misclassification of GM and WM, we extracted from this cohort all patients with large RAD lesions (>10 mL and >10% of DWI1). The core was defined as hyperintense voxels on DWI1 and DWI2. Magnetic resonance images and regions of interest (ROIs) (DWI1, core, and RAD) were normalized to a standard space using a nonlinear transformation (FMRIB Software Library version 4.1). The accuracy of normalization was assessed by visual inspection. After segmentation based on a probabilistic map (threshold=0.5) for WM, GM and cerebrospinal fluid obtained from the 3DT1 Montreal Neurological Institute template, DWI1, core, and RAD lesion ROI volumes and their WM/GM distribution were calculated using a voxel-counting algorithm (Matlab 7.9.0; Figure 1). Cerebrospinal fluid and unclassified voxels (<3%) were discarded. For each patient, we prospectively recorded age, onset-to-treatment time, and National Institutes of Health Stroke Scale score. The study was approved by the local Ethics Committee. For each patient, we compared, using paired Wilcoxon tests, the percentage of WM voxels in RAD lesions and the core and the proportion of reversibility of WM and GM voxels (eg, for WM, the number of WM voxels in RAD lesions divided by the number of WM voxels in DWI1). The relationship between the percentage of RAD lesion (RAD volume/DWI1 volume) and the percentage of WM in DWI1 was determined using linear regression (SPSS 21.0).
Results

Thirty patients were eligible (median [interquartile range] age, 62 years [53–73 years]; admission National Institutes of Health Stroke Scale score, 15 [12–18]; onset-to-treatment time, 134 minutes [105–185 minutes]). The median DWI1 and RAD lesion volumes were 65.0 mL [31.6–124.9 mL] and 23.3 mL [19.1–35.0 mL], respectively. As predicted, the percentage of WM voxels in RAD lesions (59.4% [52.8%–68.9%]) was greater than that in the core (49.6% [43.0%–57.5%]; \(P = 0.011\)). Accordingly, the probability of reversibility was significantly greater for a WM voxel than for a GM voxel (60.8% [25.5%–88.7%] versus 53.5% [21.1%–77.3%]; \(P = 0.02\)), and the percentage of RAD lesions increased with the proportion of WM present in the acute DWI lesion (\(\beta = 2.18; SE, 0.46; P<0.0001; R = 0.67\); Figure 2).

Discussion

By quantitatively assessing the WM versus GM distribution in patients with large RAD lesions, and despite the small differences in proportions observed, our study disclosed that ischemic WM voxels were significantly more prone to reverse than GM voxels. Although no previous similar study is available for a comparison, our finding is consistent with the notion that WM may be more resistant to ischemia compared with GM.\(^1\)\(^–\)\(^4\) Experimental studies also support this notion.\(^4\) In humans, although the fate of WM versus GM has rarely been studied, our results are consistent with the available data, irrespective of the imaging approach.\(^1\)\(^–\)\(^3\)\(^,\)\(^9\)\(^,\)\(^10\) For instance, a positron emission tomography study using the hypoxia tracer \(^1\)\(^8\)F-misonidazole found salvageable tissue in WM at later time points than in GM, suggesting that the former has a slower evolution toward infarction.\(^3\) At earlier time points and using perfusion DWI, the same investigators again emphasized the greater resistance of WM to ischemia.\(^3\) This is also supported by the lower perfusion threshold for infarction\(^3\)\(^,\)\(^9\) and greater autoregulatory efficiency\(^1\)\(^1\) of WM relative to GM.

Our quantitative finding that DWI reversal predominates in WM after thrombolysis confirms previous qualitative observations in the early\(^6\) or later time windows.\(^6\)\(^,\)\(^7\) Furthermore, and consistent with this finding, the percentage of RAD lesions increased with the proportion of WM included in the acute DWI lesion. As a corollary, a low fraction of WM would be expected in DWI lesions that do not exhibit reversal. We addressed this issue in a post hoc case–control study in which the 30 patients with RAD lesions used here (cases) were compared with 30 patients without RAD lesions (controls) extracted from our database to be individually matched for recanalization, DWI1 volume, and onset-to-treatment time. We found a significantly lower percentage of WM in the acute DWI lesion in patients without RAD lesions than in patients with RAD lesions (52.3% [44.6%–58.1%] versus 56.1% [49.9%–65.7%]; \(P = 0.04\)). This post hoc finding further strengthens the validity of our main observation.

The amount of WM matter in the initial DWI lesion may therefore be a significant determinant of RAD lesions, which is itself associated with early neurological improvement.\(^5\) In turn, acute DWI lesions predominantly or exclusively involving WM may be more prone to reversal and to respond to therapy than their GM counterparts. This may have bearing on the DWI lesion volume predictive of poor response to reperfusion therapy, which could be adjusted for its WM content for improved accuracy. Also, DWI lesions involving WM may have a longer time window for positive response to therapy. Finally, thresholds for core and penumbra may need adjustment for WM content.

Limitations of this preliminary study include its retrospective, single-center nature and relatively small number of patients with large RAD lesions. The results need confirmation in other populations and more subjects. Methodological limitations include the absence of individual segmentation on

![Figure 1](http://stroke.ahajournals.org/)

![Figure 2](http://stroke.ahajournals.org/)
high-resolution T1-weighted images because this sequence is not part of standard magnetic resonance stroke protocols.\(^3\)

Finally, we acknowledge that data interpretation relies on small differences in observed proportions and that the ultimate fate of RAD lesions deserves dedicated studies.

The WM predominance of DWI reversal reinforces the view that there is differential resistance of brain compartments to ischemia. This may justify, in future studies, a tissue-specific approach to improve the identification of viable tissue that could benefit from reperfusion therapy.

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**Disclosures**

None.

**References**


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