Published in final edited form as:

Stroke. 2014 November ; 45(11): 3275–3279. doi:10.1161/STROKEAHA.114.006082.

Immediate Changes in Stroke Lesion Volumes Post-Thrombolysis Predict Clinical Outcome

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Abstract

Background and Purpose—We hypothesize that reversal in DWI volume at 24 hours predicts favorable clinical outcome only if accompanied by immediate reperfusion. Our aim was to quantify the immediate DWI and MTT changes at 2 and 24 hours after IV-tPA in order to evaluate the effect of reperfusion and DWI change on outcome.

Methods—Patients were selected from the Lesion Evolution in Stroke and Ischemia On Neuroimaging Project if they had an acute MRI with evaluable DWI and PWI, were treated with standard IV-tPA, had post-thrombolysis MRI with evaluable DWI and PWI at 2 and/or 24 hours and had follow-up FLAIR MRI at discharge through 90 days. A reader measured the DWI, MTT and FLAIR volumes using a validated technique. A vascular neurologist scored the NIHSS at admit, 2 and 24 hours and the mRS at discharge, 5, 30 and 90 days. Favorable clinical outcome was defined as mRS of 0 or 1.

Results—Seventy-one patients met the study criteria with mean ($\pm$ SD) age of 71.6 ($\pm$ 16.4) years, 58% women, median admit NIHSS 9 (IQR: 4-18), median onset to triage 45 minutes (30-65) and median first MRI to IV-tPA 47 minutes (39-59). In binary multiple logistic regression analysis, younger age (OR=1.165, $p=0.014$, 95% CI: 1.031-1.316), lower admit NIHSS (OR=1.221, $p=0.012$, 95% CI: 1.045-1.427), decrease in MTT volume at 2 hours (OR=1.021, $p=0.031$, 95% CI: 1.002-1.040) and decrease in DWI volume at 24 hours (OR=1.173, $p=0.027$, 95% CI: 1.018-1.351) were significant predictors of favorable clinical outcome.

Conclusions—Reversal of the DWI volume at 24 hours due to immediate reperfusion in patients post thrombolysis is predictive of favorable clinical outcome.

Keywords

ischemic stroke; infarct size; thrombolysis; diffusion-weighted imaging; perfusion imaging

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Disclosures: None

Introduction

Several studies exploring MRI variables and their ability to predict clinical or imaging outcome post-thrombolysis in acute ischemic stroke patients have been reported.¹⁻⁶ Some studies suggest that diffusion-weighted imaging (DWI) lesion reversal occurs with reperfusion.⁷⁻⁹ Studies investigating the change of the DWI volume after thrombolysis have demonstrated a consistent correlation with clinical outcome.¹⁰ Reperfusion and the resulting size of the DWI lesion post-thrombolysis are potential markers of therapeutic efficacy and can be predictive of favorable clinical outcome.^{11,12} The EchoPlanar Imaging Thrombolytic Evaluation Trial (EPITHET)¹³, Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE)¹⁴⁻¹⁵ and Desmoteplase in Acute Ischemic Stroke Trial (DIAS)¹⁶ studies established the feasibility and utility of imaging mismatch as the penumbral target for therapy. However the measurement of stroke lesions, the amount of acute mismatch and their change across time is still problematic due to the dynamic evolution of stroke lesions, technical and quality limitations in the acquisition and limited real-time processing of DWI and perfusion-weighted imaging (PWI) in the acute stroke setting. Further understanding of the immediate changes of the ischemic and perfusion lesions is necessary to optimize the evaluation of acute mismatch and its potential as a therapeutic target and predictor of clinical outcome.

The objective of this study was to quantify the DWI and PWI changes at 2 and 24 hours after IV-tPA in order to evaluate the effect of early reperfusion and DWI lesion decrease on clinical outcome measured as latest available mRS from discharge up to 90 days. Our hypothesis is that an early decrease in DWI volume at 24 hours associated with immediate reperfusion predicts favorable clinical outcome.

Methods

Patients

This study uses data from the Lesion Evolution in Stroke and Ischemia On Neuroimaging (LESION1)¹⁷ Project which enrolled consecutive patients with an admission diagnosis of acute ischemic stroke or TIA seen between August 1999 and October 31, 2009 by the NIH Stroke Team at Suburban Hospital (SH) in Bethesda, MD and the Medstar Washington Hospital Center (MWHC) in Washington DC who met the following criteria: (1) screened with MRI within 24 hours of witnessed stroke onset and had an admission National Institutes of Health Stroke Scale (NIHSS) score > 3, or (2) had a acute MRI prior to and received an acute intervention. The appropriate Ethics and Institutional Review Boards approved the study. For this study, patients were included from the LESION1¹⁷ project if they: (1) had an acute MRI with both evaluable and positive DWI and PWI, excluding lacunar strokes, (2) were treated with standard IV-tPA, (3) had post-thrombolysis MRI with evaluable DWI and PWI at 2 or 24 hours and (4) had FLAIR at follow-up including discharge through 90 days.

Clinical Assessments

Vascular neurologists blinded to the lesion volume measurements examined all patients at every imaging time point. The primary outcome was functional status at 3 months (with last observation carried forward when the 3-month assessment was not available) using 2 cutoffs that are common in clinical trials: (1) favorable (mRS of 0 to 1) and (2) unfavorable (mRS 2) outcome.

Imaging Assessments

Vascular neurologists blinded to the clinical assessments and lesion volume measurements including reperfusion status examined all patients at the acute MRI for the site of vessel occlusion and recanalization status at 2 and 24 hours. The recanalization status was reported as complete, partial or none. The available magnetic resonance angiography (MRA) imaging series were reviewed to determine recanalization status.

Imaging Series

The MR imaging protocol utilized in this study has been published.¹⁸ MR imaging was performed using 1.5T (Twinspeed, General Electric) or 3T (Achieva, Philips) clinical scanners. The DWI was a spin-echo planar series using either 40-3.5 mm or 20-7 mm thick contiguous axial oblique slices with $b=0$ and $b=1000$ s/mm², trace or isotropically weighted, TR/TE=6000-9000/72-90 ms, acquisition matrix of 128×128-256×256, and 22-24 cm field of view (FOV). The fluid attenuated inversion recovery (FLAIR) was a high resolution series with TR/TE=9000/92-146 ms, TI=2200 ms, acquisition matrix of 256×128-256×256, using either 66-2 mm or 20-7 mm thick contiguous axial oblique slices and 24 cm FOV. The PWI was a dynamic susceptibility weighted contrast series. The parameters for the PWI gradient-echo planar series included 20 contiguous axial oblique slices with single-dose gadolinium contrast injection of 0.1 mmol/kg of gadolinium (gadolinium-DTPA; Magnevist; Bayer Schering Pharma) through a power injector using 25-40 phase measurements, TR/TE=1500-2200/45 ms, acquisition matrix of 64×64-128×128-256×256, 7 mm slice thickness, and 22-24 cm FOV. The mean transit time (MTT) maps were calculated as the first moment of the time concentration curves divided by the zeroeth moment with no arterial input correction or deconvolution. Only MTT maps were used for the perfusion measurements and reperfusion analysis. The DWI, FLAIR and PWI series were acquired co-localized over the entire brain with a superior to inferior coverage of 14 cm. The MRA acquired was an intracranial 3D TOF centered in the region of the Circle of Willis using TR/TE = 39/6.9 ms, flip-angle = 25°, matrix of 224 × 160, 24 × 18 cm FOV for an in-plane resolution of approximately 1 mm, reconstructed to 92 axial images, 1.6 mm thick with a 0.8 mm overlap.

Lesion Volume Analysis

The rater reliability statistics for the planimetric method were published elsewhere.¹⁸ Briefly, the validated watershed based method involved the semi-automated segmentation of the lesion areas on a slice-by-slice basis with the user placing seed points in these areas followed by user-driven editing using Cheshire™ (Boulder, CO). The DWI, MTT and FLAIR volumes were automatically calculated in Cheshire™ using the planimetric method

by multiplying the respective total lesion area by the slice thickness. DWI reversal was defined as reduction of > 5 ml of the follow-up DWI compared to the acute DWI volume. Complete reperfusion was defined as 90% reduction of the follow-up MTT compared to the acute MTT volume.

Statistical Analysis

The following analyses were performed: (1) clinical and imaging characteristics of all 71 study patients were tabulated. Values were reported as mean ($\pm$ SD), percentage or median (IQR 25-75) where appropriate. Spearman correlation coefficients were calculated with significant relationships reported. Nonparametric tests (Mann Whitney U or Chi-squared) were performed to compare the distributions or classifications of variables according to groups defined as patients with favorable versus unfavorable clinical outcome.

For multivariable analysis, significant variables, $p < 0.05$, were entered in binary logistic regression to identify predictors of favorable clinical outcome. The associated sensitivity and specificity values were calculated for the significant predictors.

Linear regression was performed to investigate prediction of follow-up FLAIR volume. IBM SPSS Statistics v19.0 was used for all statistical analyses performed.

Results

Clinical and Imaging Characteristics

Seventy-one patients met the study criteria with mean ($\pm$ SD) age of 71.6 ($\pm$ 16.4) years; 58% were women, the median admit NIHSS was 9 (IQR: 4-18), the median onset to triage was 45 minutes (30-65), median onset to acute MRI was 81 minutes (66-108) and median time from start of acute MRI to IV-tPA was 47 minutes (39-59) (Table). Sixty-one (86%) patients had anterior circulation and 10 (14%) had posterior circulation strokes. Patients had the following vessel occlusion sites: ACA 1% (1/71), Basilar 1% (1/71), extracranial ICA 11% (8/71), intracranial ICA 8% (6/71), M1 25% (18/71), M2 13% (9/71), PCA 4% (3/71), Vertebral 1% (1/71), none 32% (23/71) and not evaluable 1% (1/71). Twelve patients (17%), 10 (83%) anterior circulation and 2 (17%) with posterior circulation stroke, had immediate DWI reversal at 2 hours, and of these, six (8%) had sustained reversal at 24 hours. Patients at 2 and 24 hours, 13% ($n=9/71$) and 27% ($n=19/71$) respectively, had complete reperfusion. For the 9 patients with complete reperfusion at 2 hours, 7 (78%) were anterior circulation and 2 (22%) were posterior circulation strokes. For the 19 patients with complete reperfusion at 24 hours, 16 (84%) were anterior circulation and 3 (16%) were posterior circulation strokes. Patients at 2 and 24 hours, 25% ($n=18/71$) and 31% ($n=22/71$) respectively, had complete recanalization. Patients at 2 and 24 hours, 17% ($n=12/71$) and 15% ($n=11/71$) had partial recanalization, while 21% (15/71) and 18% (13/71) had no recanalization. Recanalization status was not applicable in cases with no vessel abnormality or not evaluable for 37% (26/71) and 35% (25/71) patients, respectively at 2 and 24 hours. Figure 1 compares the DWI and PWI lesion volumes across all time points for all patients versus the classification of patients with favorable clinical outcome ($n=30$) versus the patients with unfavorable clinical outcome ($n=41$).

The univariate comparison of variables according to favorable versus unfavorable clinical outcome is reported in Table. Younger, male, lower admit NIHSS, smaller acute DWI and MTT volumes, decrease in DWI and MTT volumes at 2 and 24 hours, and decrease in FLAIR volume from 5 to 90 days, were significantly associated with favorable clinical outcome. In binary multiple logistic regression analysis, younger age (per year decrease, OR=1.165, $p=0.014$, 95% CI:1.031-1.316), lower admit NIHSS (per point decrease, OR=1.221, $p=0.012$, 95% CI:1.045-1.427), decrease in MTT volume at 2 hours (OR=1.021, $p=0.031$, 95% CI:1.002-1.040) and decrease in DWI volume at 24 hours (OR=1.173, $p=0.027$, 95% CI:1.018-1.351) were significant predictors of favorable clinical outcome. In binary multiple logistic regression analysis, younger age (per year decrease, OR=1.102, $p=0.005$, 95% CI:1.03-1.18), admit NIHSS (per point decrease, OR=1.136, $p=0.02$, 95% CI:1.020-1.264) and decrease in DWI volume at 24 hours (OR=1.126, $p=0.008$, 95% CI:1.032-1.23) were significant predictors of favorable clinical outcome. Interestingly, combination of younger age (per year decrease, OR=1.111, $p=0.001$, 95% CI [1.044-1.182]) with decrease in DWI volume at 24 hours (OR=1.128, $p=0.004$, 95% CI [1.04-1.224]) yielded the best prediction of favorable clinical outcome (sensitivity of 81%, specificity of 88%) compared to the model with age and admit NIHSS (sensitivity of 68%, specificity of 72%).

Among the 43 patients with acute DWI ≤ 5 ml, those with a decrease in DWI volume at 2 hours ≤ 5 ml were more likely than those with no decrease to have a favorable outcome with mRS 0-1 (60% vs. 18%; $p=0.014$). Among the 53 patients with an acute MTT ≤ 5 ml, 42 (79%) had a decrease in MTT lesion volume > 7 ml, and 11 (21%) had an increase or no change ($p<0.001$) at 24 hours. A higher proportion of patients with reperfusion at 24 hours had a favorable outcome (45% vs. 0%; $p=0.002$), see Figure 2. Using linear regression, 24 hour DWI volume was highly correlated with follow-up FLAIR volume ($p<0.01$, $R^2=0.675$).

Discussion

The major finding of this study is that, in addition to age and acute NIHSS score, early reperfusion at 2 hours and a sustained decrease in DWI lesion volume at 24 hours are independent predictors of favorable clinical outcome after thrombolysis. This is the first study to our knowledge that the specific relationship between immediate reperfusion at 2 hours and the sustained DWI lesion volume decrease at 24 hours for prediction of favorable clinical outcome has been identified. Prior studies have shown separately that DWI reversal and reperfusion and findings have significant clinical implications indicating the importance of acute multimodal MRI in evaluation of efficacy of thrombolytic therapy.^{8,10} The percentage of thrombolytic treated patients, ~40%, with complete reperfusion is also consistent with prior studies.⁸

The study has several strengths. The imaging acquisition and analysis are comprehensive since it includes pre-thrombolysis DWI and PWI, both 2 and 24 hours post-thrombolysis and chronic FLAIR imaging. Comparable studies have included imaging protocols at prethrombolysis and 2 or 24 hours, but not both immediate post-thrombolysis time points and with limited or no PWI data.⁸⁻¹⁰ Further the relationship of the chronic FLAIR imaging for infarct growth relative to reperfusion and the 24 hour DWI volume is demonstrated.¹⁰⁻¹¹

However the additional imaging data and the range of lesion volumes in this study provides further insight into the specific acute mismatch volume and subsequent imaging changes characteristic of patients with favorable clinical outcome post-thrombolysis. In all study patients, immediate reperfusion at 2 hours and subsequent decrease in DWI volume at 24 hours in patients post-thrombolysis is the imaging changes most predictive of favorable clinical outcome. For example in patients with a substantial acute DWI lesion, defined by > 5 ml, the decrease of DWI volume at 2 hours post-thrombolysis is a significant predictor favorable clinical outcome. In patients with any reperfusion, the decrease of NIHSS and MTT volume at 24 hours post-thrombolysis are significant predictors of favorable clinical outcome.

The study also has some limitations. Although acute primary vessel involvement and recanalization status were assessed on MRA across the time points, the analysis was limited. The recanalization categorization was simply scored as complete, partial or none and specifics on proximal versus distal site of occlusion, TOAST classification and collateral circulation data were not captured. In this study, reperfusion but not recanalization was a significant predictor of favorable outcome. One possible explanation for this finding was the relatively low number of patients with complete recanalization. Further the validated measurement technique of lesion volumes in this study is time consuming and is not applicable to real-time treatment decision making in the acute stroke clinical setting. An untreated patient group for comparison purposes was not included in this study due to the limited imaging data at follow-up for these patients. Therefore the immediate lesion volume changes and their impact on clinical outcome seen in this IV tPA treated patient population are not translatable to an untreated patient population. However the acute mismatch volumes are applicable to an untreated patient population. Although not statistically significant, the patients with a favorable outcome had a much smaller median acute mismatch volume compared to those with an unfavorable outcome (see Table). The differences in acute DWI and MTT volumes between the favorable and unfavorable outcome patients support the concept of an imaging profile of patient that will most likely benefit from thrombolysis, patients with smaller DWI lesion volumes and significant MTT lesion volumes that do not exceed a certain threshold. Further the clinical utility of the immediate follow-up DWI and PWI in patients treated with thrombolysis is demonstrated to gauge the attenuation of the acute DWI lesion growth and the coincident reperfusion. The advantage of paired DWI and PWI at follow-up is evident, see Figure 2, as patients with similar acute imaging profiles may have very different follow-up imaging changes and resulting clinical outcomes. Finally the application of acute and immediate follow-up DWI and PWI in testing new thrombolytics is another advantage due to the smaller number of patients needed to compare the new thrombolytic and its effects on DWI lesion growth and immediate reperfusion with responses of standard IV-tPA in this study and others.⁸⁻¹⁰ A future study is in progress to measure the immediate changes in lesion volumes in an untreated population and to compare the clinical and imaging variables using the same favorable and unfavorable clinical outcome definitions.

In conclusion the immediate changes in lesion volume, specifically immediate reperfusion and corresponding DWI reversal are predictive of favorable clinical outcome. The role of recanalization needs further investigation. This study supports the usage of multimodal MRI

pre and post-thrombolysis for understanding the relationship between immediate lesion change and its impact on long-term clinical outcome. It provides a cohort of data on standard IV-tPA treated patients that may be used for comparison in future imaging based stroke clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: NIH

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Figure 1.

Median DWI and PWI lesion volumes from baseline, 2 hour to 24 hour time points, FLAIR lesion volume from chronic time points for patients with favorable clinical outcome (blue lines) versus unfavorable clinical outcome (red lines). Median mismatch lesion volumes at baseline are included (blue dot versus red dot).

Figure 2.

Patient (top row), 47 year old male, with admit NIHSS=4, partial reperfusion (71% reduction) with complete recanalization at 2 hours and complete reperfusion and recanalization at 24 hours with 50% reduction in DWI volume by 24 hours and outcome mRS=1. Patient (bottom row), 74 year old female, with admit NIHSS=26, partial reperfusion (24% reduction) with no recanalization at 2 hours and no change in MTT volume with no recanalization at 24 hours with significant growth in DWI volume by 24 hours with outcome mRS=6.

Table

All patients versus patients classified with favorable clinical outcome (mRS=0 or 1) versus unfavorable clinical outcome (mRS ≥ 2)

Variable	All patients (n=71)	Favorable clinical outcome (n=30)	Unfavorable clinical outcome (n=41)	Significance
Age (years,±SD)	71.6 (±16.4)	63.4 (±17)	77.6 (±13.2)	p<0.001*
Sex (n,% female)	41 (58%) female	12 (40%) female	29 (71%) female	p=0.010*
Admit NIHSS [IQR25-75]	9 [4-18]	5 [2-11]	17 [7-24]	p<0.001*
Onset (minutes) [IQR]	45 [30-65]	46 [35-65]	40 [25-65]	p=0.096
Onset to start of Acute MRI time (minutes) [IQR]	81 [66-108]	86 [69-113]	78 [64-102]	p=0.228
Acute MRI time to start of IV-tPA (minutes) [IQR]	47 [39-59]	45 [31-59]	48 [42-62]	p=0.152
Acute DWI volume (ml) [IQR]	8.4 [2.1-51.5]	4.3 [1.1-17.0]	18.1 [3.2-63.1]	p=0.021*
Acute MTT volume (ml) [IQR]	128.6 [27.2-206.9]	63.0 [0.3-156.3]	152.0 [55.1-236.7]	p=0.013*
Acute Mismatch volume (ml) [IQR]	93.4 [6.1-180.6]	40.4 [0.0-146.6]	129.5 [11.7-210.1]	p=0.077
Change in NIHSS at 2 hours [IQR]	-1 [-3-0]	-2 [-6-0]	-1 [-2-0]	p=0.213
Change in DWI volume (ml) at 2 hours [IQR]	0.9 [-1.8-4.8]	-0.1 [-4.5-1.9]	2.7 [-0.5-16.6]	p=0.005*
Change in MTT volume (ml) at 2 hours [IQR]	-26.4 [-58.9-4.4]	-27.4 [-93.2-0]	-2.7 [-46.6-27.8]	p=0.028*
Complete (< 90%) reperfusion at 2 hours (%)	9 (13%)	5 (17%)	4 (10%)	p<0.001*
Complete recanalization at 2 hours (%)	18 (25%)	7 (23%)	11 (27%)	p=0.74
Change in NIHSS at 24 hours [IQR]	-2 [-6-1]	-2 [-8-(-1)]	-1 [-4-4]	p=0.027*
Change in DWI volume (ml) at 24 hours [IQR]	5.1 [0.0-31.2]	0.5 [-1.7-9.1]	19.0 [1.1-73.1]	p<0.001*
Change in MTT volume (ml) at 24 hours [IQR]	-43.8 [-133.4-(-5.4)]	-68.7 [152.9-(-27.2)]	-41.4 [-115.7-2.0]	p=0.108
Complete (< 90%) reperfusion at 24 hours (%)	19 (27%)	12 (40%)	7 (17%)	p=0.001*
Complete recanalization at 24 hours (%)	22 (31%)	9 (30%)	13 (32%)	p=.879
Follow-up mRS [IQR]	2 [0-5]	0 [0-1]	4 [3-6]	---
Follow-up FLAIR volume at 5 to 90 days (ml) [IQR]	10.5 [0.5-45.9]	1.8 [0.0-12.6]	37.9 [8.3-65.2]	p<0.001*
Change in follow-up FLAIR volume (ml) [IQR]	0.01 [-2.9-15.5]	-0.7 [-8.3-4.3]	9.7 [-1.2-36.0]	p=0.011*