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Early Change in Stroke Size Performs Best in Predicting Response to Therapy

Alexis Nétis Simpkins, MD, PhD¹, Christian Dias, BS¹, Gina Norato, ScM², Eunhee Kim, PhD², and Richard Leigh, MD¹ on behalf of the NIH Natural History of Stroke Investigators

¹Neuro Vascular Brain Imaging Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (A.S., C.D., R.L.), United States

²Office of Biostatistics, National Institute of Neurological Disorders and Stroke, National Institutes of Health (G.N., K.E.), Bethesda, MD, United States

Abstract

Background—Reliable imaging biomarkers of response to therapy in acute stroke are needed. Final infarct volume and percent early reperfusion have been used for this purpose. Early fluctuation in stroke size is a recognized phenomenon, but its utility as a biomarker for response to therapy has not been established. This study examined the clinical relevance of early change in stroke volume comparing it with final infarct volume and percent of early reperfusion in identifying early neurologic improvement (ENI).

Methods—Acute stroke patients enrolled 2013–2014 with serial MRI scans (pre-treatment baseline, 2 hours post, and 24 hours post) who received thrombolysis were included in the analysis. Early change in stroke volume, infarct volume at 24 hours on diffusion, and percent early reperfusion were calculated from the baseline and 2 hour MRI scans were compared. ENI was defined as 4 point decrease in NIHSS within 24 hours. Logistic regression models and receiver operator characteristics analysis were used to compare the effectiveness of three imaging biomarkers.

Results—Serial MRIs of 58 acute stroke patients were analyzed. Early change in stroke volume was significantly associated with ENI by logistic regression analysis ($p = 0.048$, OR 0.93) and remained significant after controlling for stroke size and severity ($p = 0.032$, OR 0.90). Thus for every 1 mL increase in stroke volume, there was a 10% decrease in the odds of ENI, while for every 1 mL decrease in stroke volume, there was a 10% increase in the odds of ENI. Neither infarct volume at 24 hours nor percent early reperfusion were significantly associated with ENI by logistic regression. Receiver operator characteristic analysis identified early change in stroke volume as the only biomarker of the three that performed significantly different than chance ($p = 0.03$).

Corresponding Author: Alexis Nétis Simpkins, MD PhD, Address: Building 10, B1D733 MSC 1063, 10 Center Drive, Bethesda, MD 20892. Phone: 301 435 9321, Fax: 301 480 0413, alexis.simpkins@nih.gov.

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Conclusions—Early fluctuations in stroke size may represent a more reliable biomarker for response to therapy than the more traditional measures of final infarct volume and percent early reperfusion.

Keywords

Brain Imaging; Brain Ischemia; Diffusion weighted MRI; MRI; Stroke

Introduction

It is well recognized that early interventions in acute ischemic stroke improve long-term patient outcomes. However it has not been established what early biomarkers of response to therapy are most informative. Imaging biomarkers that could predict early neurologic improvement (ENI) in response to an intervention could be useful in Phase II clinical trials as well as in guiding clinical management. Magnetic resonance imaging (MRI) is an established biomarker for delineating areas of infarction with diffusion weighted imaging (DWI), identifying regional ischemia with perfusion weighted imaging (PWI), and visualizing vascular occlusion with time-of-flight angiography. The volume of restricted water movement detected on DWI 24-48 hours after stroke onset, often referred to as the final infarct volume, has been proposed as a biomarker for response to therapy.[1] Another commonly used biomarker for response to therapy is the percent of early reperfusion identified as a reduction in PWI lesion size.[2, 3] A less commonly measured biomarker for response to therapy is the early change in stroke size measured on apparent diffusion coefficient (ADC) maps immediately before and after treatment. Although it is known that infarct volumes can fluctuate after acute treatment, there is disagreement about the clinical relevance of these changes since decreases in stroke volume are typically transient. We hypothesized that early stroke volume change would provide the earliest prognostic information about response to therapy. The purpose of this study was to compare the biomarker of the change in stroke volume 2 hours after treatment with that of final infarct volume and percent early reperfusion to predict ENI in stroke patients receiving acute intervention.

Materials and Methods

Patient Population

This study was governed under the guidelines of the Declaration of Helsinki of 1975 (including the revisions in 1983), and written, informed consent was obtained from all subjects. Patients consented and enrolled in the NIH Natural History of Stroke Study titled “Evaluation, Pathogenesis, and Treatment of Patients with or at Risk for Cerebrovascular Disease (A Natural History/Disease Pathogenesis Protocol),” during the years of 2013 and 2014 were considered for this study. The institutional review board for the National Institute of Neurological Disorders and Stroke and the two enrolling hospitals (Suburban Hospital, Bethesda, Maryland and Medstar Washington Hospital Center, District of Columbia) approved this study. Briefly, the NIH Natural History of Stroke Study is an observational imaging study. The protocol for imaging study patients within the first 24 hours is described below. At both sites, standard practice is to triage all patients with suspected acute ischemic

stroke with MRI provided they do not have a contraindication to MR imaging. Gadolinium is used for perfusion imaging provided there are no contraindications to the contrast agent, such as renal dysfunction or contrast allergy. Magnetic resonance angiography (MRA) of the intracranial vessels is also obtained. Patients with an acute ischemic stroke on MRI are eligible for enrollment in the NIH Natural History of Stroke Study, including patients that do not receive gadolinium. During the first 24 hours, the patients or their legal representative are approached for consent. Patients consented prior to the 2 hour time point undergo an MRI at that time. Patients remain eligible for enrollment in the study if consent can be obtained prior to the 24 hour time point. As a result, only a subset of the total number of patients enrolled into the Natural History of Stroke Study had the imaging necessary to be part of the current analysis as described below.

MRI Parameters

Images were acquired on a 1.5T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI), a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands), or a 3T Siemens Skyra scanner (Siemens AG, Munich, Germany). Image sequences and typical parameter ranges were: Diffusion tensor imaging (TR 4461-10500msec, TE 61.6-91.3 msec, 3.5mm slice thickness, 40 slices) used to generate trace diffusion weighted images (DWI) using three orthogonal directions ($b = 0$ and 1000 s/mm^2) and apparent diffusion coefficient (ADC) maps; fluid attenuated inversion recovery (FLAIR) imaging (TR 9000 msec, TE 120-145 msec, 3.5 mm slice thickness, 40 slices); time-of-flight (TOF) MRA images (TR 18-23 msec, TE 3.43-6.8 msec, 0.75-1.4 mm slice thickness, 73-95 slices); gradient recall echo (GRE) images (TR 700-800 msec, TE 12-20.4 msec, 3.5-7 mm slice thickness, 20-40 slices); dynamic susceptibility contrast (DSC) perfusion weighted imaging (PWI) (TR 1-1.5 sec, TE 25-45 msec, 7mm slice thickness, 20 slices, 40-80 dynamics), which was collected during the injection of a weight-based dose of gadolinium (0.1 mmol/kg of gadolinium-DPTA, Magnevist; Bayer Schering Pharma, Whippany, New Jersey or gadolinium-BOPTA Multihance, Bracco Diagnostics, Monroe Township, New Jersey).

Image processing

The target population for inclusion in this study were patients who presented with a perfusion deficit; this required them to have had PWI with gadolinium as part of their initial MRI. Perfusion deficits were defined on the pre-treatment MRI by thresholding the PWI time-to-peak (TTP) maps at a 4 second delay in contrast arrival, compared to normal tissue from the contralateral hemisphere. This resulted in a region of interest (ROI) which, through co-registration methods, could be moved between image sequences and through imaging time points.[4] This enabled all MRI quantification to be performed in the native space of the scan, not on the co-registered image. Within that ROI, the volume of ADC voxels whose diffusion coefficient was less than $600 \text{ mm}^2/\text{s}$ was calculated. Early change in stroke size was measured by subtracting the pre-treatment ADC volume from the 2-hour ADC volume. For patients with reduction in their ADC volume (negative change) at the 2-hour time point, sustained lesion reversal was considered to have occurred if the 24-hour ADC volume remained less than or equal to the 2-hour ADC volume. Percent early reperfusion was calculated as the fraction of the pre-treatment PWI ROI that was no longer greater than or equal to 4 seconds on the TTP map of the 2-hour MRI. Thus, the percent early reperfusion at

2 hours reflects the degree of recanalization 2 hours after acute intervention was administered to the patient. Final infarct volume was calculated by segmenting the ROI superimposed on the 24 hour DWI into stroke and non-stroke subgroups using a k-means clustering algorithm. All image processing was done using Matlab software (Mathworks, Natick, MA). Analysis of early change in stroke size was performed in patients with pretreatment and 2 hour MRI scans. Comparison of early change in stroke size with percent reperfusion and final infarct volume was restricted to patients who had the necessary imaging for all three biomarkers.

Outcomes

National Institutes of Health Stroke Scales (NIHSS) were assessed at the time of each MRI by neurologists who are certified performing the NIHSS and undergo NIHSS training annually. Early neurologic improvement (ENI) was defined as a decrease of 4 or more points on the NIHSS from the pre-treatment assessment to the post 24-hour assessment. The pre-treatment MRI brain and time-of-flight magnetic resonance angiography (MRA) were reviewed by a vascular neurologist (A.N.S.), who was blinded to clinical outcome, for stroke location and the presence of a large vessel occlusion (LVO). LVO was defined as occlusion of the first segment of the middle cerebral artery or occlusion of the distal internal carotid artery. Re-canalization status after acute treatment was assessed by measuring the perfusion volumes on the follow up MRI scans performed 2 hours and 24 hours post thrombolysis. Additionally, a modified Rankin score (mRS) was obtained at 30 and 90 days whenever possible. For the purposes of this study, if the 90 day mRS was not available, then the 30 day mRS was used. A good functional outcome was defined as a mRS of 0 or 1.

Statistics

To evaluate whether each study measurement was significantly different between the patients with and without ENI, Fisher's exact test was used for categorical variables, and Wilcoxon Rank-Sum test was used for continuous variables. Univariate and multivariate logistic regression models were used to investigate the relationship between the change in early stroke volume as a continuous measurement and a binary outcome of ENI. The odds ratio (OR) for the early change in stroke volume and its 95% confidence interval (CI) were constructed. Multivariate logistic models were constructed by adding admission NIHSS and pre-treatment ADC lesion volume to the univariate model containing just early change in stroke volume.

Furthermore, a receiver operating characteristic (ROC) analysis[5] was performed to compare the performance of the three imaging biomarkers (percent early reperfusion, final infarct volume, and early change in stroke size between the baseline and 2 hour MRI) using the subset of patients with adequate data to test all three imaging biomarkers. Specifically, the non-parametric area under the ROC curve (AUC) of each imaging biomarker was calculated for its ability to predict ENI. Youden's J statistic was then used to define the optimal cut-point. Specificity and sensitivity were described at that cut-point for the early changes in stroke volume.

P-values less than 0.05 were considered significant. All statistical data analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 131 patients had an MRI prior to treatment with IV tPA and were subsequently enrolled into the NIH Natural History of Stroke Study. Of these, 59 patients had the necessary imaging to calculate early change in stroke, 49 had the necessary imaging to calculate percent early reperfusion, and 51 had the necessary imaging to calculate final infarct volume. Of these, data were available to calculate ENI in 58 patients. The reasons for patient exclusions are detailed in figure 1.

The demographics for the patients with and without ENI are listed in table 1. ENI occurred in 25 (43%) patients. The NIHSS on admission was significantly higher in patients with ENI. Patients with ENI also had significantly larger ADC volumes prior to treatment than patients without ENI (6.4 mL [4.2 to 19.6] versus 2.6 mL [0.4 to 9.8] respectively, p -value=0.02). The pre-treatment perfusion volumes did not differ between the groups (p =0.36). In the total population of patients, 33 (57%) had a thrombus visible on the gradient echo image that corresponded with a vascular occlusion on the MRA within either the M2 or M1 segment of the middle cerebral artery or the distal internal carotid artery. The percent reperfusion 2 hours post-acute intervention did not differ between groups (p =0.27). The percent reperfusion detected at 24 hours also did not reach statistical significance (p =0.07). Thus no clear difference in recanalization was detected between the ENI groups.

The difference between the 2 hour ADC volume and the ADC volume at baseline was significantly different between patients with ENI and without ENI (-1.5 mL [-8.7 to 0.8] versus 0.0 mL [-0.3 to 1.6], p -value = 0.03). The difference in ADC volume at 2 hours was also significantly associated with ENI in the logistic regression analysis (OR=0.93, 95% CI: [0.87, 0.99], p -value=0.048). This association remained statistically significant after adjusting for the admission NIHSS and pre-treatment ADC lesion volume (OR=0.90, 95% CI: [0.81, 0.99], p -value=0.032). This indicates that for every 1 mL increase in stroke volume at 2 hours, there is a 10% decrease in the odds of ENI, and for every 1 mL decrease in stroke volume at 2 hours there is a 10% increase in the odds of ENI.

Out of the 58 patients analyzed for the early changes in stroke volume and ENI, 33 exhibited a reduction in stroke volume two hours after treatment. Of these 33 patients, 30 had an evaluable ADC acquired at 24 hours. Only six (20%) of these patients had sustained lesion reversal at 24 hours. For the patients with a decrease in the ADC volume at 2 hours relative to the baseline ADC volume but without sustained lesion reversal (n =24), the median percent increase in ADC volume at 24 hours was 38% [8% to 61%]. Thus the clinical improvement found with decreased early stroke volume occurred despite return of a substantial portion of the original lesion in most patients. Two examples of this phenomenon are depicted in figure 2.

To compare the change in ADC volume at 2 hours with percent early reperfusion and final infarct volume, only patients with evaluable MRI sequences for each of the 3 imaging biomarkers were included, resulting in a subset of 45 patients. Figure 3 compares the ROC curves of the three biomarkers. The area under the curve (AUC) for each were: 0.682 (95% CI : [0.516, 0.848]) for early change in stroke volume; 0.617 (95% CI : [0.447, 0.787]) for percent early reperfusion; 0.532 (95% CI : [0.035, 0.712]) for final infarct volume. The AUC was higher for early change in stroke volume than for percent early reperfusion or final infarct volume, and early change in stroke volume was the only imaging biomarker that performed significantly better than AUC of 0.5 (chance), with a p-value of 0.03. The sensitivity and specificity of early change in stroke volume using the optimal cut-off were 65% and 86% respectively. Thus, approximately 14% of patients who do not have ENI using the early changes in stroke volume will be incorrectly identified as having ENI as a false positive.

ENI was used in this study as a marker of response to therapy/acute ischemic stroke treatment, however modified Rankin scale (mRS) is the typical measure used for assessing functional outcome in clinical trials. Of the 46 patients in this study with available mRS, 14 (70%) of patients with ENI had a good functional outcome (mRS of 0 or 1) compared to 8 (32%) of the patients without ENI (p-value = 0.02).

Discussion

It is intuitive to think that the size of a patient's stroke would be representative of their response to therapy. In the absence of effective reperfusion, strokes will grow in size. However, there is an anecdotal clinical observation that patients who receive acute stroke treatments, such as IV tPA or embolectomy, and appear clinically to respond to therapy, often still have a sizable infarct on their DWI when performed at 24 hours. It was this clinical observation that led us to question how good final infarct volume is as a biomarker for response to therapy.

Using final infarct volume based on the 24 hour DWI, as was recently recommended by the STAIR imaging guidelines,[1] the lesion measurement is based on both T2 signal change as well as restricted diffusion. Thus, the resulting biomarker reflects both cytotoxic and vasogenic edema. When calculating early change in stroke volume based on ADC values during the first two hours, only changes in diffusion restriction are included in the biomarker. Thus, early change in stroke volume gives a more direct measure of cellular function and injury, and this may account for our findings.

In our study, we found that early change in stroke volume was better than the more commonly used MRI biomarker, final infarct volume, in identifying patients who had responded to therapy clinically. Moreover, we found that in patients with reversal of their ADC lesion, the decrease in volume is rarely sustained, which is in agreement with prior descriptions of this phenomenon.[6-9] However, unlike prior studies that reported minimal clinical benefit to unsustained lesion reversal,[10] [11, 12] we found that early change in stroke volume was associated with clinical improvement, with patients being 10% more likely to have early neurologic improvement for every 1mL decrease in stroke lesion volume

from baseline to the 2 hour time point. This discrepancy may come from the assumption of prior investigators that the incorporation of transient stroke lesion volumes into final infarct volume was equivalent to a lack of clinical benefit, or that the clinical improvement occurs secondary to resolution of a perfusion deficit. In our study, the pre-treatment perfusion volumes were not different between patients with or without ENI, and resolution of the perfusion deficit did not perform well in identifying ENI. This may be due to the fact that resolution of the perfusion deficit does not capture the underlying injury. Unlike the perfusion deficit, the ADC volumes were significantly different, with larger volumes in patients who had ENI. This may have been why the baseline NIHSS were also higher in ENI group. It may be that patients with larger lesions had more potential tissue to salvage (reverse) and thus a higher likelihood for ENI with reperfusion. We opted to use a decrease in NIHSS of 4 or more to delineate ENI. Given that small improvements in NIHSS could be unrelated to thrombolysis, improvement in very mild stroke patients (NIHSS<3) were not included in the ENI group.[13]

The patients in our cohort, and those in other studies with similar findings,[6, 7, 14-16] were imaged and treated in early time windows. Since early change in stroke volume is closely associated with successful early reperfusion, the benefit of early reduction in stroke lesion volume may not be detected if recanalization and imaging are acquired at later time points. Although it has previously been reported that non-sustained reversal of stroke lesions has clinical benefit,[6, 7, 16] we are the first to compare early changes in stroke lesion volume with final infarct volume as an imaging biomarker for clinical response to therapy.

One interpretation of our finding is that, when looking at 24-hour DWI, not all strokes are the same. Animal data support the hypothesis that final infarct volume does not capture early pathophysiologic changes. An MRI study of rats undergoing transient middle cerebral artery occlusion found that animals exposed to 30 and 60 minutes of cerebral ischemia demonstrated transient reversal of the ADC lesion, while animals with 2.5 hours did not reverse.[17] This may explain why other human studies have reported less frequent transient reversal than was detected in our study.[8] Hematoxylin and eosin staining of tissue with transient reversal has demonstrated incomplete areas of neuronal cell loss and preservation of astrocytes. Capillaries in areas with transient reversal are less likely to stain for markers of stress than tissue that did not have transient reversal. Tissue in regions of lesion growth or lack of ADC fluctuation is characterized by necrosis and complete infarction.[18] Thus the DWI lesions on an MRI scan 24 hours after a stroke may represent a heterogeneous population of lesions with varying clinical outcomes that are not best captured by final infarct volume.[19] MRIs collected at 24 hours after the event may lack the critical information to determine if there has been a clinical benefit. If this is true, then it is important to consider this when designing clinical trials that are planning to use imaging biomarkers of response to therapy.

The strength of this study is that it was based on a pre-specified clinical hypothesis, however there are several limitations to this study. Our sample size was small, and we do not know if we were powered to rule out an association between response to therapy and final infarct volume; rather, it is more likely, that with a larger sample size, a significant association would be identified. Larger studies looking at long-term outcome have found a significant

relationship between final infarct volume and modified Rankin score at 90 days.[20] Here we did not directly look at association of the imaging biomarkers with functional outcome (mRS), as the focus was on response to therapy. It is important not to conflate these measures; however for the population we studied, ENI was associated with good functional outcome. Although our study supports the use of early change in stroke volume as a better biomarker for response to therapy, this study alone does not establish superiority over conventional measures such as final infarct volume or percent of early reperfusion. In addition, only patients able to tolerate serial imaging were included in this study, which may have resulted in some selection bias. We used a fully automated pipeline to perform the biomarker measurements. The advantage of this approach is that it is highly reproducible and avoids human bias. However, removing the human component can result in increased noise in the measurements. Additionally, our biomarker definitions may be different than those used in other studies, thus our results may not be comparable to their findings. Imaging of the collateral circulation, which may also be a predictor of ENI, was not performed in this study. We also acknowledge that our study findings will need to be further investigated in different patient populations.

This study gives preliminary evidence that early changes in stroke volume should be collected as a biomarker in future clinical trials for which imaging is being used to assess response to therapy. Although MRI is not the standard imaging modality for screening for acute treatment in acute ischemic stroke, it has been successfully utilized at specialized research centers [21] and in previous multicenter clinical trials.[3] Future studies should evaluate these findings in a larger cohort.

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Figure 1.
Population Flow chart. ENI, Early Neurologic Improvement; MRI, Magnetic Resonance Imaging; NIHSS, National Institute of Health Stroke Scale.

Figure 2.

Panels A and C show the imaging of 2 patients with early neurologic improvement (ENI) and panels B and D are of 2 patients without ENI. Notice that at the 2-hour time point, for the patients with ENI, the apparent diffusion coefficient (ADC) lesion has reversed, while for the patients without ENI, the ADC lesion persists. By 24 hours, both patients show a substantial DWI lesion volume, however the patient with decreased early change in stroke size has a sustained clinical improvement.

Figure 3.

Receiver operator characteristic (ROC) curves for each of the imaging biomarkers are displayed. Only early changes in stroke volumes performs significantly better than chance for predicting early neurologic improvement with a p-value of 0.03. Moreover, the area under the curve (AUC) was highest with early change in stroke size (AUC = 0.6818), while final infarct volume (AUC = 0.5316) and percent early reperfusion (AUC = 0.6166) were lower. ECS = early change in stroke size; PER = percent early reperfusion; FIV = final infarct.

Table 1

Patient Demographics

Variables	Overall (N=58)	ENI (N=25, 43%)	No ENI (N=33, 57%)	p Value
Median Age, years (IQR)	75 (59-84)	72 (63-78)	78 (56-85)	0.39
Gender (male), n (%)	31 (53%)	14 (56%)	17 (52%)	0.79
Median Baseline NIHSS, (IQR)	10 (5-18)	14 (9-17)	7 (3-18)	0.04*
Stroke Risk Factors, n (%)				
Atrial Fibrillation	25 (43%)	14 (56%)	11 (33%)	0.11
Diabetes Mellitus	13 (22%)	8 (32%)	5 (15%)	0.20
Hypertension	45 (78%)	21 (84%)	24 (73%)	0.36
Hyperlipidemia	21 (36%)	10 (40%)	11 (33%)	0.78
MRI				
Median SD to IV tPA, (IQR)	114 (90-165)	97 (90-145)	126 (92-169)	0.25
Median SD to MRI, (IQR)	92 (59-139)	76 (59-113)	95 (64-139)	0.44
LMCA stroke, n (%)	23 (40%)	12 (48%)	11 (33%)	0.29
LVO, n (%)	22 (38%)	9 (36%)	13 (39%)	1.00
Acute ADC volume, (median [IQR]) mL	4.9 [1.1-15.0]	6.4 [4.2-19.6]	2.6 [0.4-9.8]	0.02*
Acute TTP volume, (median [IQR]) mL	49.7 [14.8-80.3]	56.5 [34.0-75.0]	45.5 [1.9-114.7]	0.36
Median Early Changes in Stroke Volume mL, (IQR) ^a	-0.1 (-1.9-1.2)	-1.5 (-8.7-0.8)	0.0(-0.3-1.6)	0.03*
Median Final Infarct Volume mL, (IQR) ^b	9.8 (1.9-24.5)	9.7 (4.6-20.9)	11.0 (0.7-34.1)	0.95
Median Percent Early Reperfusion at 2 hours %, (IQR) ^c	65 (41-94)	84 (47-94)	54 (35-95)	0.27

Early Changes in Stroke Volume (apparent diffusion coefficient imaging (ADC) volume at baseline - ADC volume 2 hours); ENI, Early Neurologic Improvement; IQR, Interquartile Range; Final Infarct Volume (diffusion weighted lesion volume at 24 hours); IV, Intravenous; LVO, Large Vessel Occlusion; LMCA, Left Middle Cerebral Artery; N, Sample Size; SD, Symptom Discovery; TTP, Time to Peak;

^a sample size of 58,

^b sample size of 51,

^c sample size of 49.