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Abstract:

Background: Major anterior circulation ischemic strokes caused by occlusion of the distal internal carotid artery (ICA) or proximal middle cerebral artery (MCA) or both account for about one-third of ischemic strokes with mostly poor outcomes. These strokes are treatable by IV-tPA and endovascular methods. However, dynamics of infarct growth in these strokes are poorly documented. The purpose was to help understand infarct growth dynamics by measuring acute infarct size with DWI at known times after stroke onset in patients with documented ICA/MCA occlusions.

Methods: Retrospectively, we included 47 consecutive patients with documented ICA/MCA occlusions who underwent DWI within 30h of stroke onset. Prospectively, 139 patients were identified using the same inclusion criteria. DWI lesion volumes were measured and correlated to time since stroke onset. Perfusion data was reviewed in those who underwent perfusion imaging.

Results: Acute infarct volumes ranged from 0.41-318.3ml. Infarct size and time did not correlate (R^2=0.001). The majority of patients had DWI lesions that were less than 25% the territory at risk (<70ml) whether they were imaged < or >8h after stroke onset. DWI lesions corresponded to areas of greatly reduced perfusion.

Conclusions: Poor correlation between infarct volume and time after stroke onset suggests that there are factors more powerful than time in determining infarct size within the first 30h. The observations suggest that highly variable cerebral perfusion via the collateral circulation may primarily determine infarct growth dynamics. If verified, clinical implications include the possibility of treating many patients outside traditional time windows.

Introduction

Acute ischemic stroke is the fourth leading cause of death in the United States and the leading cause of severe disability in adults. [1] Cerebral artery occlusions of the terminal internal carotid artery (ICA) and/or the proximal middle cerebral artery (MCA) represent 30-40% of all acute ischemic strokes, but account for the majority of poor outcomes. [2] Current treatment approaches for these strokes are commonly restricted by the time elapsed since stroke onset. For intravenous tissue plasminogen (IV tPA), the currently approved treatment window is 3-4.5 hours from the time of stroke onset. [3, 4] For intra-arterial therapy (IAT) the time window is typically 0-6 hours for thrombolysis and 0-8 hours for mechanical therapies. [5] This adherence to time windows is driven by the idea that there is rapid infarct growth while ischemia is left untreated [6] and that treatment efficacy rapidly decreases with time. [7-10]

A limitation of the current approach is that it does not take into consideration patient-specific cerebrovascular physiology. [11] While quantitative estimates of the pace of neuronal loss in human ischemic stroke may be applicable on a population level, the actual rate of neuronal loss in patients with proximal anterior circulation artery occlusion (ACO) strokes may vary considerably from patient to patient, and is influenced by a number of factors, most importantly the effectiveness of cerebral perfusion via the collateral circulation in maintaining the reversibly threatened, hypoperfused but still viable tissue outside of the infarct. [12-14] Recently the time-based approach has been challenged as treatments have been shown to be effective outside the traditional time windows. [15, 16]

The dynamics of infarct growth in patients with proximal ACO strokes are not well documented. Experimental animal stroke models suggest that the most common pattern of infarct growth is logarithmic. [17, 18] Although infarct growth patterns in human brain have not specifically been evaluated, linear infarct growth is commonly assumed. [6] The purpose of this study was to gain insights into infarct growth dynamics in patients with documented proximal ACO by measuring acute infarct size using diffusion weighted MRI up to 30 hours after stroke onset.

Methods

Patient selection

This study consisted of retrospective and prospective components. Both components were compliant with the Health Insurance Portability and Accountability Act (HIPAA) and were approved by our institutional review board (IRB).
The retrospective study utilized data from a published study by Copen et al. [19]In that study, all patients who presented to the emergency department (ED) of our hospital from June 2005 through December 2006 with symptoms suggesting an acute stroke syndrome were screened. We also prospectively identified patients who presented to our hospital ED with stroke symptoms from January 2008 to October 2009.

Inclusion criteria were: 1. Patients presented to the ED with acute symptoms of stroke within 30 hours of symptom onset. 2. MR imaging including a DWI scan demonstrating an acute anterior circulation infarct; 3. CT angiography (CTA) or MR angiography (MRA) of the head demonstrating a proximal anterior circulation artery occlusion (i.e. terminal ICA and/or proximal MCA (M1 and/or M2 origin); 3. All imaging was performed before any thrombolytic or other

recanalization therapies. Stroke onset time for each patient this study was the estimate entered in the clinical record by the stroke neurologist caring for the patient. Patients who had unknown time of stroke onset or had "wake-up" strokes were not included in the study.

Imaging acquisition

All imaging studies were requested by ED physicians based on clinical need and were not influenced by these studies.

Computed tomography angiography

In the retrospective study, CTA was performed from the C6 vertebral body level through the circle of Willis following the injection of 100–140 ml of Isovue 61.2 g/100 mL (Bracco Diagnostics, Princeton, NJ) at a rate of 3 ml/s. Imaging was triggered 25 seconds after contrast injection (40 seconds for patients with atrial fibrillation). Immediately afterward, a second set of images was obtained from the aortic arch to the skull base. The parameters were 2.5-mm slice thickness, 1.25-mm reconstruction interval, 140 kV, 220–250 mA, and 0.75:1 pitch.

In the prospective study, CT angiography was performed from the vertex to the aortic arch following injection of 80–120 ml of Isovue 370 at a rate of 3.5 ml/s. SmartPrep (GE Medical Systems, Milwaukee, WI) was used with a region of interest 1 cm below the carina covering the lumen of the ascending aorta. Scanning began 10 seconds after the region of interest reached 75 HU. The parameters were 1.25-mm slice thickness, 0.625-mm reconstruction interval, 120 kV, 350–800 mA, and 0.516:1 pitch.

Magnetic resonance imaging

MR imaging was performed on a 1.5 T Signa whole body scanner (GE Medical Systems). Axial DWI were obtained using single-shot, spin echo echoplanar imaging with the following parameters: TR 5000 ms; TE 80 to 110 ms; b-value 1000 s/mm2; field of view 22 cm; matrix size 128x128, zero-filled to 256 x 256, and slice thickness of 5 mm with a 1-mm inter-slice gap. As many slices as needed to cover the entire brain were acquired. For each slice a sequence including an image without diffusion gradients plus high-gradient-factor images in six directions were acquired. This was repeated five times and resulted in 35 images for each slice and a total imaging time of less than 4 minutes. Double inversion pulses were used to reduce eddy current effects. MRA images of the head were acquired using a three dimensional time-of-flight technique with 25° flip angle, TR/TE of 36/6.8 ms, 18-cm field of view, and a 512 x 512 matrix. One hundred and eleven transverse images were reconstructed with a section thickness of 1.4 mm and spacing of 0.7 mm.

Post processing image analysis

In the retrospective study, lesions on DWI maps were outlined visually by a research technologist. In the prospective study, DWI abnormalities were outlined visually by two research fellows. All analyses were performed using a semi-automated commercially available image analysis program (Analyze 8.0; AnalyzeDirect, Overland Park, KS). These were done blinded to time of stroke onset and the locations of arterial occlusion. Diffusion lesion volumes were calculated using the b=1000 diffusion weighted images with the apparent diffusion coefficient maps used for confirmation of reduced diffusion. Regression analysis was performed to assess inter-rater reliability for the 2 individuals who measured the DWI lesion volumes of the prospective cohort. The analysis was based on 41 of 139 prospective cohort patient data sets

analyzed by both reviewers. The analysis revealed a slope of 1.09, intercept of 1.5 ml, R^2=0.95

with p < 0.0001, indicating acceptable inter-rater reliability.

Statistical analysis

Two tailed Spearman's rank analyses were performed to assess for a significant

correlation between time from ictus and DWI lesion volume. A finding was deemed significant if

the p value was <0.05. Statistical analyses were performed using SPSS statistical software

(release 20.0 for Windows; SPSS, Chicago, IL).

Results

Table 1 shows demographic and imaging data. Of the 47 patients in the retrospective

cohort, there were 29 (62%) patients with DWI infarct volumes ≤ 70 ml, which is less than 25%

of the territory at risk. In the prospective cohort of 139 consecutive patients, 103 (74%) had DWI

infarct volumes ≤ 70 ml. For the total sample of 186 patients, acute infarct volumes ranged from

0.41 to 318.3 ml. Figure 1 shows representative diffusion weighted MR images of the first and

then every eleventh case of the prospective data set. This figure provides a visual illustration of

the randomness of infarct size with respect to time. Figure 2 is a scatter plot of acute infarct size

with respect to time since stroke onset for all 186 patients; there was no correlation between

infarct volume and time (R^2=0.001 and p=0.712). Mean infarct volumes were not significantly

different when grouped into temporal cohorts (Supplemental Table I).

We investigated the possible roles of occlusion site heterogeneity and uncertainty of time

of stroke onset. A subset of 56 patients (mean age: 70 years, SD +/- 15, males: 34) with only

MCA M1 occlusions were evaluated. The patients in this subset appeared well within 30 minutes

of when their stroke was discovered. Similar to the entire group, there was no correlation

between diffusion lesion volume and time since stroke onset ($R^2 = 0.017$ and $p = 0.342$). There were also no correlations between time after stroke onset and DWI lesion volume in patients with only M1 occlusions (Supplemental Figure I), ICA occlusions (Supplemental Figure II), and T occlusions (Supplemental Figure III). The most homogenous subset consisted of 46 patients with witnessed stroke onset and with M1 segment MCA occlusions. A scatter plot of these patients is shown in Figure 3. There was no correlation between DWI lesion volume and time since witnessed stroke onset ($R^2 = 0.000$ and $p = 0.959$). Finally, we investigated potential bias by the 2 research fellow that calculated lesion volumes in the prospective cohort (Figures IV and V) finding similar results for both individuals.

To explore the range of infarct growth rates in these patients, we estimated the rate of infarct growth assuming linearity from time of stroke onset to the point of imaging. Figure 4 illustrates the very wide range of infarct growth rates calculated in this fashion. The mean rate for the retrospective cohort was 23 ml/hr with a standard deviation of 36 ml/hr and a range from <1 to 170 ml/hr. The mean rate for the prospective cohort was 12 ml/hr with a standard deviation of 15 ml/hr and a range from <1 to 77 ml/hr. For those in the prospective cohort with witnessed stroke onset, the mean growth rate was 12 ml/hr (SD of 13.8 ml/hr) and a range of <1 to 69 ml/hr. Some patients had very rapid apparent infarct growth. For example, of 139 patients with M1 occlusions, 30 who were imaged within 8 hours after ictus had DWI lesion volumes >70ml. Assuming linear lesion growth, 16 of these patients would have had DWI volumes >70ml if they had been imaged even 2 hours or less after ictus (Supplemental Figure SIV). We thus estimate that ~12% of patients with MCA occlusions in our study had DWI lesion volumes >70ml by 2 hours after stroke onset.

To help understand the low correlation between DWI lesion volume size and time after stroke onset, imaging data was further reviewed in all patients who also had a perfusion MRI (PWI) study performed. A total of 128 patients met these criteria. In the retrospective cohort, all 47 patients had PWI. . In this cohort all patients with a small DWI lesion volume (<70ml) had identifiable perfusion beyond the lesion, although it was abnormal with a mean transit time (MTT)/DWI mismatch of >100% in all such patients [20]. A review of all 71 patients in the prospective cohort also revealed that in all patients who had DWI abnormalities that were significantly smaller than the territory at risk, perfusion was observable beyond the diffusion abnormality, and collateral circulation vessels were well seen on the CTA. In all patients whose collateral vessels were not well seen by CTA, and who had very reduced perfusion shown by PWI, the DWI lesion involved virtually the entire territory at risk. Figure 5 illustrates these observations in 2 patients with right MCA occlusions who were scanned ~6 hours after stroke onset.

Discussion

There were 3 major findings in patients with proximal anterior circulation arterial occlusions: a lack of correlation between DWI lesion size and time after stroke onset; a relatively small size of these infarcts in the majority of patients; and a very wide range of infarct growth rates, assuming linear growth. These findings suggest that there are factors more important than time in determining the infarct size within the first 24 hours. One potential factor that could explain all of the observations is a very wide variability in the cerebral perfusion via the collateral circulation accompanying a major anterior circulation occlusion.[12-14, 19]

We considered potential confounders. One possibility was heterogeneity in occlusion sites. However, the same lack of correlation persisted when we evaluated patients with only M1, terminal ICA and T occlusions. Another possible confounder was low precision in the estimated time between stroke onset and imaging. However, when we examined the data from patients who had witnessed stroke onset, again we found no correlation between time and diffusion lesion volume. This absence of correlation would be expected if there is large variability in the cerebral perfusion via the collateral circulation in proximal ACO patients.

The high proportion of patients who presented with infarct volumes < 70 ml may have important implications for treating stroke patients. Indeed the majority of patients had these relatively small volumes even after 8 hours after stroke onset. Since the MCA territory typically comprises 300 ml or more of the cerebrum, the findings indicate that 3/4 or more of potentially endangered tissue may still be viable many hours beyond the typical time cut-off for endovascular treatment, which is commonly 8 hours or less from the time last seen well. Thus these patients are potentially eligible for treatment. These data also support prior reports that have suggested that time alone does not provide an accurate or complete picture of stroke pathophysiology.[11, 15, 19] We also estimated that a significant proportion of patients had DWI lesion volumes >70ml by 2 hours after stroke onset, which would also have important implications on whether to proceed with thrombolytic therapy at early time points. It may be possible to use markers other than time, such as a tissue-based marker such as one contingent on differences in the diffusion and FLAIR signal as is being currently tested in the MR WITNESS trial (see at clinicaltrials.gov/show/NCT01282242).

It is often assumed that infarct growth is linear.[6] However infarct growth is logarithmic in animal stroke models.[17, 18] There are few published studies examining infarct growth in

humans, but in a study from our group in which patients were imaged several times over the first few days after stroke onset, we found that more than 80% of patients with MCA occlusions the diffusion abnormality grew very little over 24 hours whether or not there was a persistence of the occlusion. [21] This was most consistent with a logarithmic growth pattern. Even assuming a linear pattern of infarct growth, we found a very wide distribution of growth rates that ranged from less than 1 ml/hr to over 70 ml/hr (see also Figure 4). The widely quoted average rate of neuronal loss of 1.9 million neurons/min corresponds to an infarct growth rate of 5.4 ml/hr [6] which is approximately half the average rate for the patients in this study. This difference may be explained by the fact that only major anterior circulation occlusion stroke patients are considered in the current study. But the unexpected observation of a wide range of infarct growth rates suggests that there may be many patients with slow infarct growth rates that may benefit from treatment targeting the occluded vessel.

The findings presented here are best explained by wide variations in the cerebral perfusion provided by the collateral circulation. In all patients who had diffusion abnormalities that were smaller than the territory at risk, we observed evidence for perfusion beyond the diffusion abnormality that was provided by collateral circulation observed on the CTA. When the collaterals appeared poor by CTA, there was poor perfusion on PWI and the DWI lesion was noted to involve virtually the entire vascular territory at risk. However, other factors such as degree of ischemic preconditioning, systemic blood pressure and blood glucose may contribute to individual differences in infarct growth rates. Further research on this is needed.

In acute ischemic stroke due to proximal anterior circulation occlusions, a smaller infarct volume at presentation is the single best predictor of functional outcome in patients.[22] Yoo et al demonstrated that in patients with anterior circulation stroke undergoing endovascular therapy,

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those with initial infarct volumes < 70 ml who underwent early recanalization had the best clinical outcomes and the least infarct growth.[23] Additional studies have identified a volume of > 70 ml as highly predictive of poor clinical outcome irrespective of the time of presentation. [24, 25] However, the 70ml volume threshold is in the early stages of validation and further investigations may prove that another infarct core volume larger or smaller than 70ml is superior. It is also important to note that while there is general agreement that the size of the core infarct is an important factor in patient outcomes, it has been suggested that there may be better predictors of outcomes such as certain perfusion measurements.[26-29]

Currently, intravenous thrombolytic therapy is administered in only 1% - 7% of cases (high performing centers approach 15-20%), with most patients ineligible because they present outside the 3 - 4.5 hour treatment window.[30-33] Proximal anterior circulation artery occlusions may respond well to intra-arterial thrombolysis and mechanical thrombectomy; however these treatments are also typically restricted by adherence to time windows of 6 and 8 hours respectively from the time of stroke onset.[5] In the pooled analysis of the MERCI and Multi MERCI trials there was no association between time (to treatment or reperfusion) and outcomes, and 40% of the patients reperfused at >/=6.9 hours achieved independent functional outcomes. [34] Other studies have demonstrated an extension of the 3-4.5 hour window for a novel thrombolytic agent up to 9 hours without a significant increased complication of intracranial hemorrhage.[16] However, large randomized trials have not been performed using these approaches. While this study was not designed to evaluate longitudinal growth of infarct size at various time points post stroke onset, a prior study by our group demonstrated stability of diffusion/perfusion MRI abnormalities, in a series of patients with ICA or proximal MCA occlusions that persisted in a majority of the patients up to 24 hours. [21]

In light of the results of these previous studies, our finding that many patients imaged >8 hours after stroke onset have small infarct volumes, suggests opportunities for treatment outside traditional time windows. Our study does not establish that all patients with small infarct volumes would benefit from treatment. It is possible that patients presenting late may have altered tissue physiology that puts them at additional risk. It may be that their collaterals are so good that their final infarcts will remain small without revascularization. Clearly, additional studies are needed to evaluate outcomes in patients treated outside traditional time windows. Nonetheless our study adds to the body of literature that suggests that with recent developments in neuroimaging, time since onset of stroke may not be the only or the most important factor for determining who should be considered for treatment.

Conclusions

There is a lack of correlation between infarct volume and time after stroke onset in patients with proximal anterior circulation occlusion strokes that is best explained by wide variations in perfusion via the collateral circulation, although other factors may also be contributors. Some of these patients have large infarcts even at very early time points. However, most of these patients have small ischemic lesions, regardless of the time since symptom onset, and this suggests that it may be possible to treat many more patients outside traditional time windows.

Disclosures:

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Figure Legends
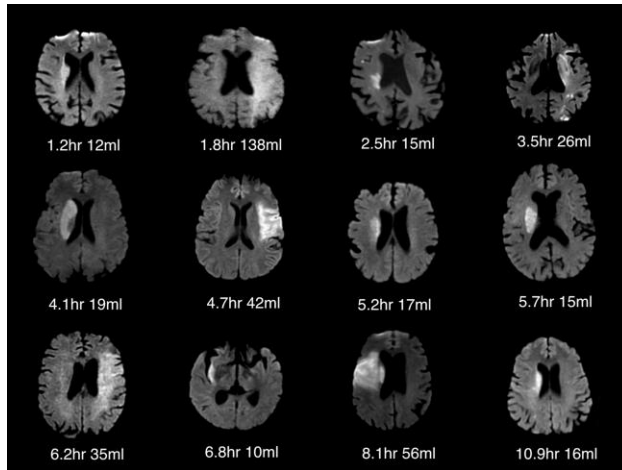
Figure 1. Representative diffusion weighted images. The images are from the prospective data set and are listed in order of imaging time after stroke onset.   The first and then every 11th case of the prospective data set are shown. Time from stroke onset and DWI lesion volumes are listed under each image. A relationship between time since ictus onset and DWI volume is not apparent. Small infarct volumes (<50ml) are observed in 10 of 12 patients.
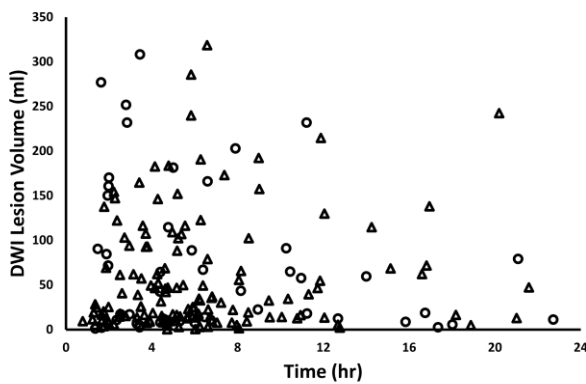
Figure 2. DWI lesion volume versus estimated time since stroke onset. A scatter plot of all stroke cases (N=186) that includes the DWI lesion volume from an MRI study performed at an estimated time after stroke onset. Open circles are from the retrospective cohort and the triangles are from the prospective cohort.
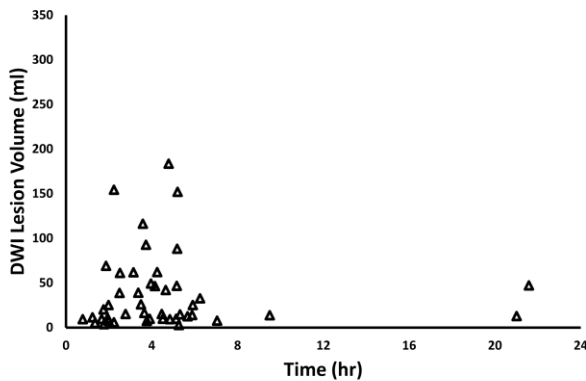
Figure 3. DWI lesion volume versus time scatter plot for patients with witnessed stroke onset and M1 occlusion only. Lesion volumes are plotted against time since stroke onset in 46 patients (mean age: 69 y, SD +/- 14, males: 25). No significant correlation was observed ($R^2 = 0.000$ and P value = 0.959).
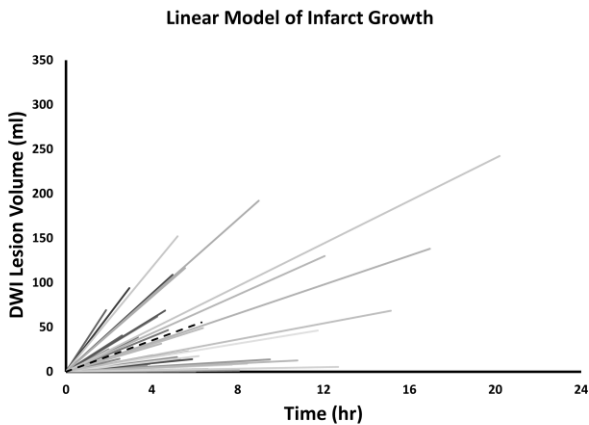
Figure 4. Linear model of infarct growth. Depicted are the estimated growths of infarcts assuming linearity for every third patient of the prospective cohort (47 of 139 cases). The dotted line represents average infarct growth of all the prospective cases, 12 ml/hr. Each line stops at the time of imaging after stroke onset for that patient.
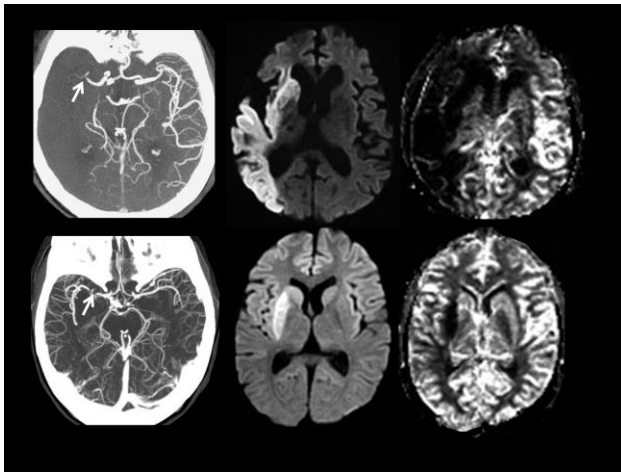
Figure 5. Diffusion lesion volume and perfusion via collateral circulation. The images are from two patients that were imaged ~6 hours after stroke onset. Both patients had a right MCA M1 occlusion (arrows). Upper row images are from a patient with a large DWI lesion that

encompasses nearly the entire right MCA territory (top middle) that has very low CBF (top right) and very few collateral vessels on CTA (top left). The lower row images are from a patient with a small DWI lesion confined to the region of the right basal ganglia (lower middle). The remainder of the right MCA territory in this patient has normal CBF (bottom right) and robust collateral vessels on CTA (bottom left).

Tables

Table 1. Demographic and imaging data

Retrospective cohort	All	DWI lesion ≤ 70 ml	DWI lesion > 70ml
Number (%)	47 (100%)	29 (62%)	18 (38%)
Age (Mean; SD)	68; 18.5	69; 17.1	67; 20.9
Male; Female	22; 25	13;16	9;9
DWI volume (median; range)	43.7; 1.2 - 308.3	12.2; 1.2 – 67.1	163.4; 71.8 - 308.3

Prospective cohort	All	DWI lesion ≤ 70 ml	DWI lesion > 70ml
Number (%)	139 (100%)	103(74%)	36 (26%)
Age (Mean; SD)	69; 15.6	71; 15.1	66; 17
Male; Female	75;64	55;48	20;16
DWI volume (median; range)	28.5; 0.41 - 318.5	16.6; 0.4 – 69.3	133.8; 71.9 – 318.5

DWI = diffusion weighted images; SD: standard deviation; Age in years; DWI volume in ml

Supplemental Methods:

For the total sample of 186 patients, the mean infarct volume was 61 ml and was similar when grouped into 3-hour temporal cohorts (Table I). There were no significant differences in diffusion abnormality volumes between the temporal cohorts (ANOVA p=0.98). Using 70 ml as a threshold, the majority of patients fell under this threshold regardless of whether they were imaged less than or more than 8 hours after stroke onset.

To further address the possible roles of occlusion site heterogeneity, the distribution of DWI volumes versus time after stroke onset in patients with MCA, distal ICA and "T" (carotid terminus, proximal MCA and proximal ACA) occlusions was evaluated. There was no

relationship between the DWI lesion volumes and time since stroke onset in any of these subsets. Figures I-III illustrate these findings.

There was high inter-rater reliability between the two research fellows in measuring DWI maps (R^2=0.95 with p < 0.0001). Figures IV and V illustrate the distribution of DWI lesion volume with respect to time after stroke onset in subsets of the prospective cohort whose volumes were measured by each of the two research fellows. There was no correlation between the DWI lesion volumes and time since stroke onset in either of the two subsets as is clearly illustrated in the figures.

Figure VI illustrates linear model of infarct growth in all patients with M1 occlusion, a large DWI lesion volume (>70 ml) and presenting within 8 hours after stroke. Assuming a linear DWI lesion growth, approximately half of these patients would have had a rapid infarct growth with DWI lesion volumes larger than 70 ml within the first 2 hours after stroke onset. This means that approximately 1 out of 10 patients with MCA occlusion in our study had a rapid infarct growth. These patients might be at high risk of treatment complications even within the accepted time windows.
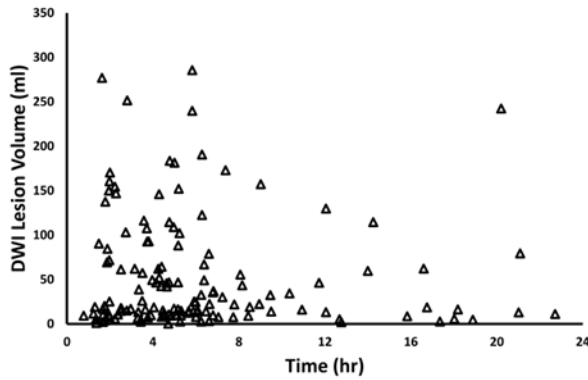
Supplemental Tables:

**Table I.** Mean and Median DWI volumes grouped into temporal cohorts

Time (hr)	N	Mean DWI volume (ml)	Median DWI volume (ml)	Range (ml)	IQR
0 - 3	42	65	23	276	97
> 3 - 6	68	62	41	308	80
> 6 - 9	37	60	30	318	56
>9- 12	16	69	43	219	68
> 12- 15	8	43	13	128	96
> 15 - 18	7	53	62	135	63
>18	8	53	15	237	64

DWI: diffusion weighted images; IQR: interquartile range
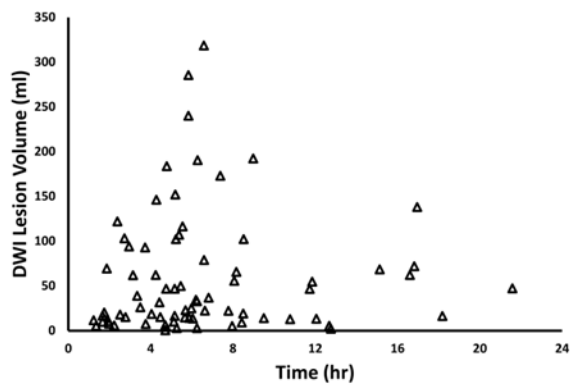
Supplemental Figures and Figure Legends:

Figure I. Distribution of DWI lesion volume with respect to time after stroke onset in all patients with M1 occlusion (N=139; R^2 =0.003; p=0.53).
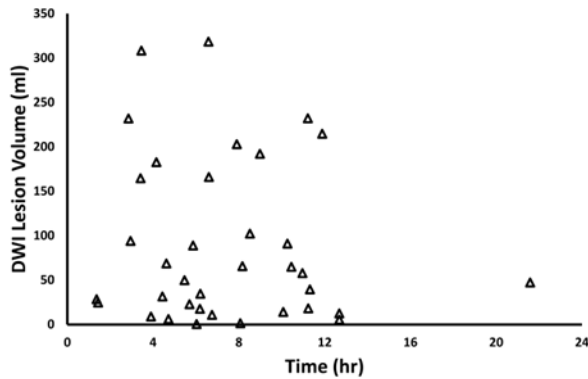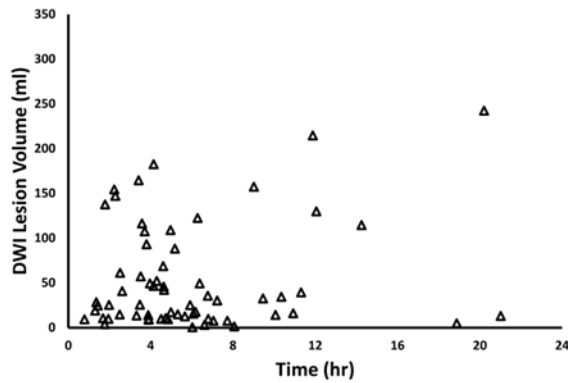

Figure II. Distribution of DWI lesion volume with respect to time after stroke onset in all patients with terminal ICA occlusion (N=36; R^2 =0.01; p=0.52).
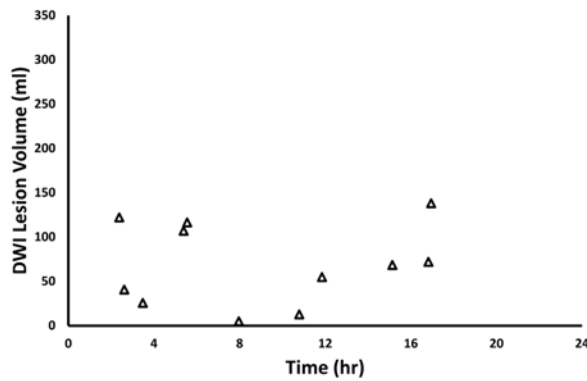
Figure III. Distribution of DWI lesion volume with respect to time after stroke onset in all

patients with a T lesion (N=11; R^2 =0.01; p=0.77).

Figure IV. Distribution of DWI lesion volume with respect to time after stroke onset in patients

from the prospective cohort whose volumes were measured by the first research fellow (N=75;

R^2 =0.001; p=0.83).

Figure V. Distribution of DWI lesion volume with respect to time after stroke onset in patients

from the prospective cohort whose volumes were measured by the second research fellow

(N=64; R^2 =0.034; p=0.15).
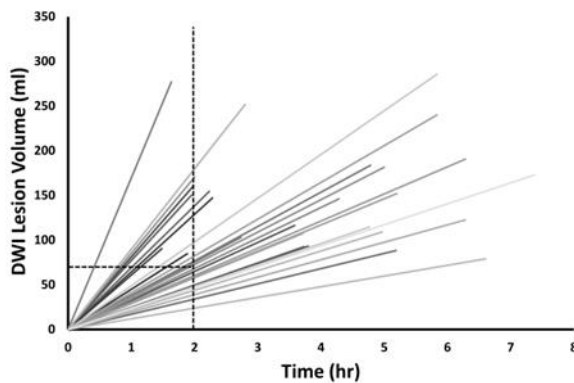
Figure VI. Estimation of number of patients with DWI lesion volumes >70 ml by 2 hours after

stroke onset. An estimate of infarct growth was made assuming linearity for all patients with M1

occlusion and a DWI lesion volume > 70 ml who were imaged within 8 hours after stroke onset

(N=30). The vertical dashed line is at 2 hours after stroke onset; the horizontal dashed line is at a

DWI lesion volume of 70 ml. A total of 16 patient of the 30 patients had an estimated DWI

lesion volume of >70ml by 2 hours after stroke.