Ischemic Core and Hypoperfusion Volumes Predict Infarct Size in SWIFT PRIME

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Objective: Within the context of a prospective randomized trial (SWIFT PRIME), we assessed whether early imaging of stroke patients, primarily with computed tomography (CT) perfusion, can estimate the size of the irreversibly injured ischemic core and the volume of critically hypoperfused tissue. We also evaluated the accuracy of ischemic core and hypoperfusion volumes for predicting infarct volume in patients with the target mismatch profile.
Methods: Baseline ischemic core and hypoperfusion volumes were assessed prior to randomized treatment with intravenous (IV) tissue plasminogen activator (tPA) alone versus IV tPA + endovascular therapy (Solitaire stent-retriever) using RAPID automated postprocessing software. Reperfusion was assessed with angiographic Thrombolysis in Cerebral Infarction scores at the end of the procedure (endovascular group) and Tmax > 6-second volumes at 27 hours (both groups). Infarct volume was assessed at 27 hours on noncontrast CT or magnetic resonance imaging (MRI).
Results: A total of 151 patients with baseline imaging with CT perfusion (79%) or multimodal MRI (21%) were included. The median baseline ischemic core volume was 6ml (interquartile range = 0–16). Ischemic core volumes correlated with 27-hour infarct volumes in patients who achieved reperfusion ($r = 0.58$, $p < 0.0001$). In patients who did not reperfuse (<10% reperfusion), baseline Tmax > 6-second lesion volumes correlated with 27-hour infarct volume

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($r = 0.78$, $p = 0.005$). In target mismatch patients, the union of baseline core and early follow-up Tmax > 6-second volume (ie, predicted infarct volume) correlated with the 27-hour infarct volume ($r = 0.73$, $p < 0.0001$); the median absolute difference between the observed and predicted volume was 13ml.
Interpretation: Ischemic core and hypoperfusion volumes, obtained primarily from CT perfusion scans, predict 27-hour infarct volume in acute stroke patients who were treated with reperfusion therapies.

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Early prediction of infarct volume in ischemic stroke patients is challenging because ischemic lesions evolve over time in response to many variables, including the adequacy of collateral circulation, and the timing and degree of reperfusion achieved.[1–3] Patients with very poor collaterals exhibit rapid infarct growth; these patients have been identified as having a "malignant" profile on computed tomography (CT) perfusion or multimodal magnetic resonance imaging (MRI).[4,5] Patients with more favorable collaterals typically have ischemic core lesions that are considerably smaller than the region of hypoperfusion. These patients have been designated as having the "target mismatch profile" (TMM) and have been proposed to be excellent candidates for reperfusion therapies.[6,7]

Previous studies have demonstrated that the diffusion-weighted imaging (DWI) lesion volume obtained on MRI immediately prior to reperfusion can provide a good estimate of the volume of tissue that will progress to infarction despite prompt and complete reperfusion.[8] However, due to the limited availability and time delays associated with obtaining acute MRI at many centers, CT scanning is the predominant imaging modality used to assess acute stroke patients. Recently, data have emerged suggesting that appropriately thresholded CT perfusion-based cerebral blood flow (CBF) maps can provide an estimate of the irreversibly injured volume similar to the acute DWI lesion in acute stroke patients.[9–11]

Dynamic susceptibility contrast magnetic resonance (MR) perfusion imaging, with appropriate thresholds applied, has been shown to provide a reasonably accurate estimate of the volume and location of critically hypoperfused tissue that is likely to progress to infarction if early reperfusion does not occur. To identify hypoperfused tissue, the DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) and EPITHET (Echoplanar Imaging Thrombolysis Evaluation Trial) studies used the perfusion parameter "time to maximum of tissue residue function" (Tmax) and documented that a Tmax contrast arrival delay of > 6 seconds (Tmax > 6 seconds) identifies ischemic tissue that is likely to become irreversibly injured if reperfusion does not occur.[12,13] In addition, quantitative positron emission tomography and xenon CT blood flow studies have confirmed that a Tmax threshold in the range of 5 to 6 seconds predicts penumbral CBF values.[14,15] Recent studies have documented that there is excellent agreement between MRI and CT perfusion for identifying Tmax > 6-second lesions.[16]

The accuracy of MRI using DWI (core) and residual hypoperfusion (Tmax > 6 seconds) volumes for the prediction of final infarct volume was prospectively assessed in the DEFUSE 2 study, a cohort of consecutive patients treated with endovascular therapy. The combination of the baseline DWI lesion with the brain regions that had Tmax > 6-second lesions on early postprocedure MRI predicted the 5-day infarct volume in TMM patients with a median absolute error of 15ml.[8]

SWIFT PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) offered a unique opportunity to examine the accuracy of early brain imaging, primarily with CT perfusion, to estimate the size of the irreversibly injured ischemic core and the volume of critically hypoperfused tissue. We also evaluated the accuracy of ischemic core and hypoperfusion volumes to predict infarct volume.

Patients and Methods

The methodology and main results of SWIFT PRIME have been published.[17] In this prospective randomized study, >80% of the enrolled patients had CT perfusion or MRI scans with DWI and perfusion prior to randomization to treatment with intravenous tissue plasminogen activator (tPA) alone versus tPA plus endovascular stroke therapy with Solitaire stent-retriever (start of endovascular procedure within 6 hours of symptom onset). The protocol for the study received prior approval by the appropriate institutional review boards, and informed consent was obtained from each subject.

A minimum of 8cm of brain coverage was required for the CT perfusion scans. An MRI (including a fluid-attenuated inversion recovery [FLAIR] sequence and a perfusion sequence) or noncontrast CT and CT perfusion was repeated 27 hours after stroke onset in most of the patients. For inclusion in this prespecified analysis, subjects were required to have a technically adequate baseline MRI or CT perfusion scan (to determine the ischemic core volume) and a noncontrast CT or MRI at 27 hours (to determine the 27-hour infarct volume). A wide variety of CT/MRI scanners were used; the most common were GE (Milwaukee, WI) Lightspeed VCT, Siemens (Erlangen, Germany), Toshiba (Tokyo, Japan) Aquilion One, and Philips (Best, the Netherlands) Ingenuity.

During the initial phase of SWIFT PRIME, enrollment was restricted to patients with the TMM profile, defined as MRI- or CT-assessed ischemic core lesion volume $\leq$ 50ml, Tmax $>$ 10-second lesion $\leq$ 100ml, mismatch volume $\geq$ 15ml, and mismatch ratio $>$ 1.8. After 71 patients were enrolled, the protocol was modified to make perfusion imaging optional; however, the majority of patients continued to have perfusion imaging performed. Sites were encouraged to continue to follow the TMM criteria for patient selection, but after the revision a limited number of patients with the malignant profile were enrolled (among the first 71 patients, only 1 had the malignant profile). The malignant profile was predefined as an MRI- or CT-assessed core infarct lesion volume $>$ 50ml and/or a Tmax $>$ 10-second lesion $>$ 100ml.

Initial baseline core lesions and Tmax $>$ 6-second lesion volumes were generated in real time during the study using fully automated software (RAPID; iSchemaView, Menlo Park, CA), which was installed at the study sites.[18] During the later phase of the study, 8 patients had CT perfusion or multimodal MRI at sites that did not have RAPID installed; these cases were postprocessed with RAPID.

CT perfusion protocols for each site were adjusted to harmonize acquisition parameters. Criteria were brain coverage of at least 8cm, temporal sampling resolution no more than 1.8 seconds, tube voltage = 80kVp, Volume CT dose index (CDTIvol) $<$360mGy, scan duration between 70 and 90 seconds, reconstructed slice thickness = 5mm and no gap or overlap, high iodine concentration contrast agent (e.g. Omnipaque 350 or Isovue 370), injection flow rate between 4 and 6 ml/s, and amount of contrast injected between 40–50ml, with no scan delay after bolus injection. Allowed scan modes used were: burst mode (GE, Toshiba, Philips), jog mode (Philips) or dynamic helical shuttle (Siemens). For CTs with a detector width $<$8cm, either 2 CT perfusion runs or dynamic helical shuttle mode were required. Iterative reconstruction methods were avoided to reduce variability between vendors. MR protocols for 1.5T and 3T were also optimized; DWI sequences required diffusion encoding in 3 principal directions from which an isotropically diffusion-weighted image was computed for subsequent analysis. The b values were 0 and 1,000s/mm^2. Parallel imaging was used to reduce geometric distortion, except on GE scanners, where residual aliasing causes erroneous apparent diffusion coefficient (ADC) artifacts. Other criteria included whole brain coverage, slice thickness $\geq$ 5mm, and scan duration $<$ 90 seconds. MR perfusion was carried out with gradient-echo echo planar imaging sequences. The sequence repetition time and thus the temporal sampling resolution was 1.8 seconds. The number of 5mm slices that could be fit within this sampling time varied between scanners and their hardware from 14 to 25 slices. Flip angle was chosen to be approximately 80° to maximize signal. Echo time was 45 milliseconds at 1.5T and 30 milliseconds at 3T.

For patients who had a baseline CT perfusion scan, the ischemic core lesion was identified by the RAPID software as tissue with a $>$70% reduction in CBF compared to normally perfused tissue. This threshold was based on a study of 103 acute stroke patients who underwent DWI immediately after CT perfusion (the median time from stroke onset to CT perfusion was 185 minutes, and time between completion of CT and start of MRI was 36 minutes). The volumetric accuracy (median absolute error) of the CT perfusion for predicting the DWI lesion was optimal at a relative CBF threshold of $<$0.30 ($a > 70\%$ reduction).[19] For patients who had an MRI at baseline, the ischemic core was defined as a lesion with an ADC $< 620 \times 10^{-6}$ mm^2/s; this threshold was identified as optimal based on an analysis of 51,045 diffusion-positive voxels from patients enrolled in the DEFUSE study.[20]

When necessary, the SWIFT PRIME imaging core laboratory corrected the automated Tmax volume assessments to remove artifacts. The baseline scan was coregistered with the 27-hour follow-up perfusion scan to create the union of the core and the follow-up Tmax $>$ 6-second volume. Infarct volume at 27 hours was assessed by manually outlining the subacute FLAIR lesion or outlining the subacute hypodense lesion on noncontrast CT (window settings of approximately 35–45HU width and 35–45HU level). Regions of hemorrhagic transformation were included in the infarct volume. If both a CT and MRI were both performed at approximately 27 hours, then the volume from the MRI lesion was selected. These manual outlines were performed prior to unblinding the treatment assignments.

For patients in the endovascular arm, early endovascular reperfusion was defined as achieving a modified Thrombolysis in Cerebral Infarction (TICI) reperfusion score of 2b–3 during the procedure. For both groups, 27-hour reperfusion was defined based on the reduction in the total Tmax $>$ 6-second lesion volume between baseline and 27 hours. Percentage reperfusion was calculated as the difference between baseline Tmax $>$ 6-second lesion volume and the 27-hour Tmax $>$ 6-second volume divided by the baseline Tmax $>$ 6-second volume.

Part 1: Relationships between Baseline Core and Hypoperfusion Volumes and 27-Hour Infarct Volumes

To assess the association between ischemic core lesion volume and the Tmax $>$ 6-second volumes and 27-hour infarct volume, patients were separated into 3 groups based on the degree of reperfusion obtained: (1) $>$ 90% reduction in the Tmax $>$ 6-second lesion volume between baseline and 27 hours (including both the endovascular and tPA-alone patients); (2) early endovascular reperfusion (TICI = 2b–3 at end of procedure, endovascular patients only); and (3) a "no reperfusion" group, defined as $<$ 10% reperfusion at 27 hours (or TICI = 0–1 during the procedure if no 27-hour perfusion scan was performed).

For patients with reperfusion, as defined above, the initial infarct core volume was compared with the 27-hour infarct volume. For patients in the no reperfusion group, the 27-hour infarct volume was compared with the baseline Tmax $>$ 6-second lesion volume (coregistration of the 27-hour scan with the baseline CT perfusion scan was performed in 3 patients in whom the baseline CT perfusion slab did not include a substantial portion of the infarct). These analyses were performed separately for patients with the TMM profile and the malignant profile as well as for both groups combined. Infarct growth

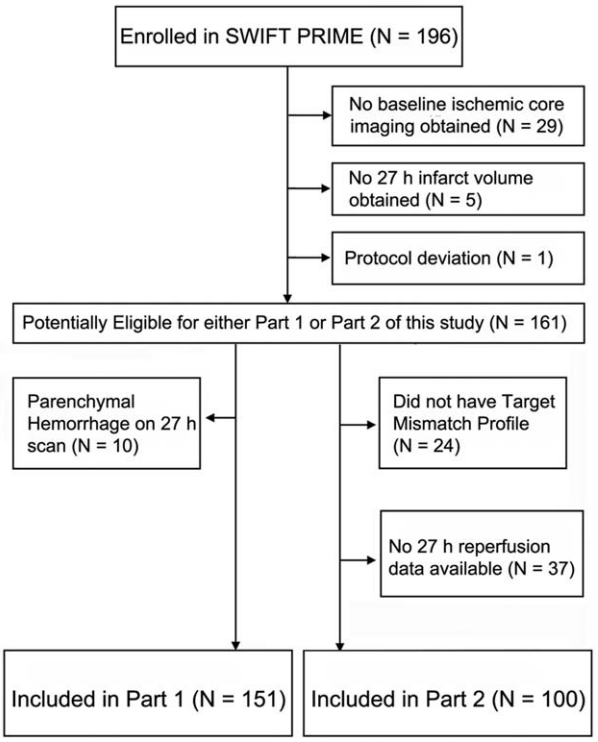


FIGURE 1: Consort diagram.

(ie, 27-hour infarct volume − baseline ischemic core volume) was also assessed and stratified on the time elapsed between the baseline imaging and when endovascular reperfusion (TICI = 2b–3) was achieved (endovascular patients only). Patients with a definite or possible parenchymal hemorrhage (PH 1 or 2) identified by the imaging core laboratory were excluded from Part 1; patients with hemorrhagic infarction (HI) at 27 hours were included.

Part 2: Prediction of 27-Hour Infarct Volume in Target Mismatch Patients

For all target mismatch patients (without exclusion for PHs), the union of baseline ischemic core with the 27-hour follow-up Tmax > 6-second lesion (predicted 27-hour infarct volume) was compared with the actual 27-hour infarct volume (on MR FLAIR or noncontrast CT). A multivariate model was constructed to evaluate whether selected baseline and post-treatment variables influenced the accuracy of the prediction of 27-hour infarct volume. The following variables were included in the model: age, baseline National Institutes of Health Stroke Scale, baseline glucose, history of diabetes, treatment group, TICI score, PH, and HI.

Statistical Analyses

Descriptive statistics, correlation coefficients, and zero-intercept linear regression analysis were used to assess baseline ischemic core and 27-hour infarct volumes as well as the relationship between predicted and actual volumes. Due to non-normality of the data, median values and interquartile ranges were calculated and are presented, rather than means and standard deviations. Spearman nonparametric rho was used to assess correlations between variables, and Wilcoxon rank sum test was used to compare results for subgroups within the patient population. Because 27-hour lesion volumes can be larger or smaller than core volumes at baseline as well as predicted volumes, absolute values were used for descriptive summaries of differences between volumes.

Results

A total of 161 patients with both baseline ischemic core imaging and a 27-hour MRI or CT scan were eligible for this study. Of these 161, 10 patients were excluded from Part 1 because of a PH 1 or 2 hematoma on the 27-hour scan (Fig 1). For Part 2, all TMM patients with 27-hour reperfusion assessment (no exclusions for hemorrhage) are included. The baseline scan was obtained at a median of 2.8 hours after symptom onset (interquartile range [IQR] = 1.6–4.1), and the "27-hour" follow-up scan was obtained at a median of 28.1 hours after symptom onset (IQR = 26.0–30.6).

The baseline characteristics of the patients included in Part 1 and Part 2 of the study are presented in Table 1. Characteristics of these patients did not differ significantly when compared to the entire SWIFT PRIME population. For patients eligible for Part 1, baseline imaging was performed with CT perfusion in 119 (79%), and obtained a median of 150 minutes (IQR = 90–239) from symptom onset. Multimodal MRI was performed at baseline in 32 (21%), and obtained a median of 236 minutes (IQR = 188–264) from symptom onset. The median processing time to generate the RAPID maps was 189 seconds (IQR = 121–321). Follow-up imaging (at 27 hours) was performed with MRI in 86 (57%) and CT in 65 (43%). The median baseline core volume (n = 151) was 6ml (IQR = 0–16), median baseline Tmax > 6-second lesion volume (n = 151) was 114ml (IQR = 68–155), and the median 27-hour infarct volume (n = 151) was 30ml (IQR = 13–78).

Sixty-two patients (87%) in the endovascular group achieved TICI = 2b–3 reperfusion; in these patients there was a significant correlation between early ischemic core volume and final infarct volume ($r = 0.46$; $p = 0.0002$), with a median absolute difference of 15ml (Table 2). The median absolute difference was 11ml for patients with target mismatch profile (n = 51), and 45ml for patients with the malignant profile (n = 10), $p = 0.002$. The median difference was smaller for patients with TICI = 3 reperfusion (11ml, n = 49) compared to TICI = 2b (32ml, n = 13), $p = 0.001$. For patients with TMM the median differences were 9ml for the 41 patients with TICI = 3 and 29ml for the 10 patients with TICI = 2b, $p = 0.003$.

Fifty endovascular patients (83%) and 20 patients in the tPA-alone group (43%) achieved > 90% reperfusion based on Tmax > 6-second hypoperfusion volumes at 27

TABLE 1. Demographic and Clinical Characteristics of the Patients

Characteristic	Part 1, n = 151	Part 2, n = 100
Age, yr	65.7 ± 12.2 [n = 150]	65.9 ± 12.8 [n = 99]
Male sex	47.0% (71/151)	45.0% (45/100)
NIHSS score, median {IQR}	16.0 {13.0, 20.0} [n = 151]	16.0 {12.5, 19.0} [n = 100]
Systolic blood pressure, mmHg, median {IQR}	150.0 {135.0–167.0} [n = 151]	146.0 {131.5–165.0} [n = 100]
Serum glucose, mg/dl	130.2 ± 41.9 [n = 151]	129.9 ± 49.9 [n = 100]
Site of IV tPA, outside hospital	37.7% (57/151)	36.0% (36/100)
Time from onset to start of IV tPA, min, median {IQR}	114.0 {83.0–151.0} [n = 151]	118.5 {85.5–152.5} [n = 100]
ASPECTS, median {IQR}	9.0 {8.0–10.0} [n = 151]	9.0 {8.0–10.0} [n = 100]
Site of intracranial artery occlusion		
ICA	13.4% (19/142)	12.9% (12/93)
M1 MCA	76.8% (109/142)	77.4% (72/93)
M2 MCA[a]	9.9% (14/142)	9.7% (9/93)
Side of occlusion, left	46.2% (67/145)	47.4% (45/95)
Time from stroke onset to randomization, min, median {IQR}	196.0 {136.0–263.0} [n = 151]	211.0 {142.0–264.5} [n = 100]
Time from stroke onset to groin puncture, min, median {IQR}	225.0 {168.0–274.0} [n = 81]	230.0 {172.0–274.0} [n = 53]
Time from ED arrival to groin puncture, min, median {IQR}	90.0 {66.0–120.0} [n = 81]	98.0 {74.0–125.0} [n = 53]
Time from qualifying image to groin puncture, min, median {IQR}	53.0 {40.0–79.0} [n = 81]	66.0 {40.0–85.0} [n = 53]

Plus–minus values are means ± standard deviation. There are no significant differences between the groups.
[a]Classified as M1 occlusions by the treating site at time of study entry but as M2 occlusions by the core laboratory.
ASPECTS = Alberta Stroke Program Early CT Score; ICA = internal carotid artery; IQR = interquartile range; IV = intravenous; MCA = middle cerebral artery; NIHSS = National Institute of Health Stroke Scale; tPA = tissue plasminogen activator.

hours (see Table 2). These patients had 27-hour infarct volumes that were substantially smaller compared with patients who did not achieve reperfusion (16 vs 124ml, $p < 0.0001$, Fig 2). Patients who achieved > 90% reperfusion had a significant correlation ($r = 0.58$, $p < 0.0001$, Fig 3A) between baseline ischemic core volumes and 27-hour infarct volumes (endovascular group, median difference = 13ml; tPA-alone group, median difference = 14ml). One patient with > 90% reperfusion had a 27-hour infarct volume that was substantially larger (245ml larger) than their baseline ischemic core volume of 24ml (see Fig 3A and 4C); this patient had the malignant profile with a Tmax > 10-second volume of 177ml at baseline. Target mismatch patients with >90% reperfusion had a 9ml median difference between the baseline core volume and the 27-hour infarct versus 38ml in malignant profile patients ($p = 0.004$) (see Table 3).

The median time between baseline imaging and obtaining endovascular reperfusion (TICI = 2b–3) was 100 minutes. Endovascular patients who achieved TICI = 2b–3 reperfusion faster than the median time (n = 30) had a median infarct growth of 12ml versus 15ml in patients who were reperfused at or later than the median (n = 33), $p = 0.42$.

Among patients with baseline CT perfusion imaging, the median difference between the baseline core volume and the 27-hour infarct volume in patients with >90% reperfusion at 27 hours was 10ml versus 17ml in patients who had baseline imaging performed by MRI ($p = 0.12$).

Among all 151 patients, there were 17 (11%) who had a 27-hour infarct volume that was smaller than the baseline ischemic core volume (14 with baseline CT perfusion and 3 with baseline MRI). The median difference

TABLE 2. Baseline and 27-Hour Ischemic Lesion Volumes in Patients with Reperfusion

Patients	Outcome								
	Median Baseline Core Volume: Both Groups, ml (IQR) [No.]	Median 27-Hour Infarct Volume: Both Groups, ml (IQR) [No.]	Absolute Volume Difference: Both Groups, ml (IQR) [No.]	Median Baseline Core Volume: tPA Alone, ml (IQR) [No.]	Median 27-Hour Infarct Volume: tPA Alone, ml (IQR) [No.]	Absolute Volume Difference: tPA Alone, ml (IQR) [No.]	Median Baseline Core Volume: Solitaire + IV tPA, ml (IQR) [No.]	Median 27-Hour Infarct Volume: Solitaire + IV tPA, ml (IQR) [No.]	Absolute Volume Difference: Solitaire + IV tPA, ml (IQR) [No.]
Patients who achieved TICI 2b–3	4 (0–13) [62]	18.7 (8.9–48.9) [62]	14.8 (4.9–33.7) [62]	—	—	—	4 (0–13) [62]	18.7 (8.9–48.9) [62]	14.8 (4.9–33.7) [62]
Patients with > 90% reperfusion at 27 hours	3 (0–14) [70]	15.9 (6.8–44.5) [70]	12.9 (5.3–30.4) [70]	3.5 (2–18) [20]	18.3 (6.95–45.45) [20]	13.8 (5.95–26.6) [20]	3 (0–12) [50]	15.5 (6.1–44.5) [50]	12.9 (4.8–30.4) [50]
Patients with > 90% reperfusion at 27 hours and baseline imaging done with CT perfusion	3 (0–14) [56]	14.5 (5.9–37.65) [56]	10.2 (4.4–22) [56]	3 (2–18) [19]	16.8 (6.9–36.2) [19]	12.8 (5.9–21.5) [19]	3 (0–11) [37]	14.4 (5.7–39.1) [37]	9.1 (3.8–22.4) [37]
Patients with > 90% reperfusion at 27 hours and baseline imaging done with MRI	7.5 (2–13) [14]	22.2 (14.5–55.3) [14]	16.7 (8.8–39.3) [14]	—	—	—	7 (2–12) [13]	20.4 (14.5–46.7) [13]	16 (8.8–33.7) [13]

CT = computed tomography; IQR = interquartile range; IV = intravenous; MRI = magnetic resonance imaging; TICI = Thrombolysis in Cerebral Infarction; tPA = tissue plasminogen activator.

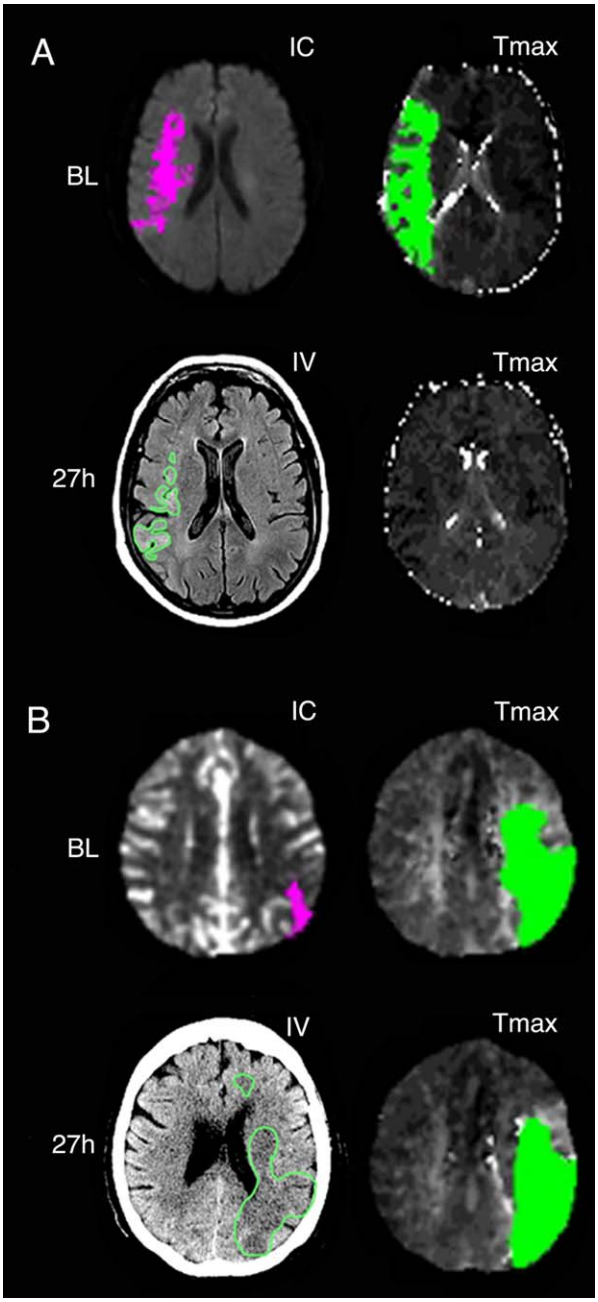


FIGURE 2: Examples where 27-hour infarct volume matches predicted infarct volume. (A) The baseline (BL) core lesion volume of 24ml (pink) is similar to the 27-hour infarct volume (20ml, outlined in green) following complete reperfusion. (B) The patient did not reperfuse, and the 27-hour infarct volume of 64ml (outlined in green) is similar to the 60ml Tmax > 6-second volume at 27 hours (solid green). IC = ischemic core; IV = infarct volume.

between the baseline ischemic core and 27-hour infarct volumes in these patients was 4ml (IQR = 2–5).

Among the 70 patients with > 90% reperfusion at 27 hours, 58 had 27-hour infarct volumes larger than the baseline core volume; the median difference was 15ml in these patients (see Figs 3 and 4). Among these patients, hemorrhagic transformation (rated as HI 1 or 2 by the Imaging Core laboratory) was a common finding; patients who had a ≥15ml difference between core and 27-hour volume had a 66% rate of HI compared with 14% in patients who had a <15ml difference ($p = 0.0001$). Among the 70 patients who had > 90% reperfusion, the median difference between the baseline core and 27-hour infarct volumes was 8ml for patients with no HI versus 32ml for patients who had HI ($p = 0.0001$).

Twelve patients (endovascular and tPA groups combined) had < 10% reperfusion (or TICI = 0–1); in these patients the correlation between baseline Tmax > 6-second perfusion volume and 27-hour infarct volume was $r = 0.78$; $p = 0.005$ (Fig 5A). The absolute median difference between the baseline Tmax > 6-second volume and the 27-hour infarct volume was 39ml. Two patients had 27-hour infarct volumes that were substantially smaller than the baseline Tmax > 6-second lesion volume (see Fig 5A). One of these patients was in the interventional group and did not have a 27-hour perfusion scan to clarify whether reperfusion occurred after the end of the procedure. The other was a control group patient who had a Tmax > 6-second lesion volume of 66ml at baseline and 63ml at 27 hours. The 27-hour infarct volume was 15ml and increased to 29ml at day 4.

Part 2

In target mismatch patients (n = 100), the union of baseline core and 27-hour follow-up Tmax > 6-second volumes (ie, predicted infarct volume) strongly correlated with the actual 27-hour infarct volume ($r = 0.73$, $p < 0.0001$, Fig 6); the median absolute difference between the observed and predicted volume was 13ml (IQR = 6–31); 71% had a predicted volume that was within 25ml of their actual 27-hour infarct volume. Among patients with CT perfusion imaging at baseline (n = 76), the union of baseline core and the 27-hour follow-up Tmax > 6-second volumes (predicted infarct volume) strongly correlated with the actual 27-hour infarct volume ($r = 0.77$, $p < 0.0001$); median absolute difference was 11ml.

Several patients from the tPA-alone group who did not achieve reperfusion had 27-hour infarct volumes that were smaller than predicted (see Fig 5). Three of these patients had subsequent unscheduled follow-up scans obtained (within 7 days); the infarct volumes obtained from these later scans were larger than the 27-hour volumes by 14ml, 20ml, and 21ml.

The multivariate model demonstrated that PH (no PH more accurate than having a PH, $p < 0.0001$) and endovascular reperfusion (TICI = 3 more accurate than 2b or TICI not measured, $p = 0.004$) were the variables

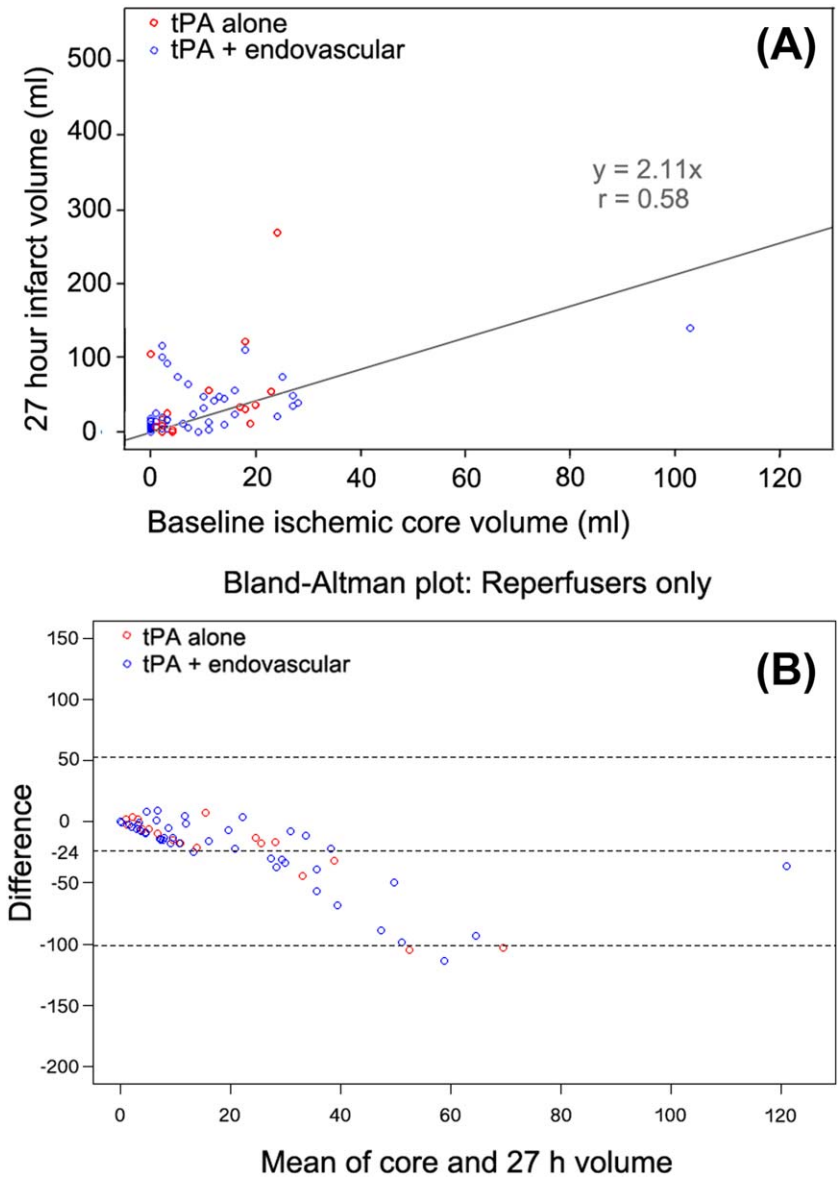


FIGURE 3: Scatter plot (A) and Bland–Altman plot (B) comparing the baseline ischemic core volume with the 27-hour infarct volume in patients with >90% reperfusion. For the Bland–Altman plot, the y-axis represents the baseline ischemic core volume − 27-hour infarct volume; therefore, negative values indicate that the 27-hour volume is larger than the baseline ischemic core volume. For the Bland-Altman plot, the bias is −24.2ml (95% confidence interval = −33.6 to −14.8). tPA = tissue plasminogen activator.

significantly associated with accuracy of prediction of 27-hour infarct volume.

Discussion

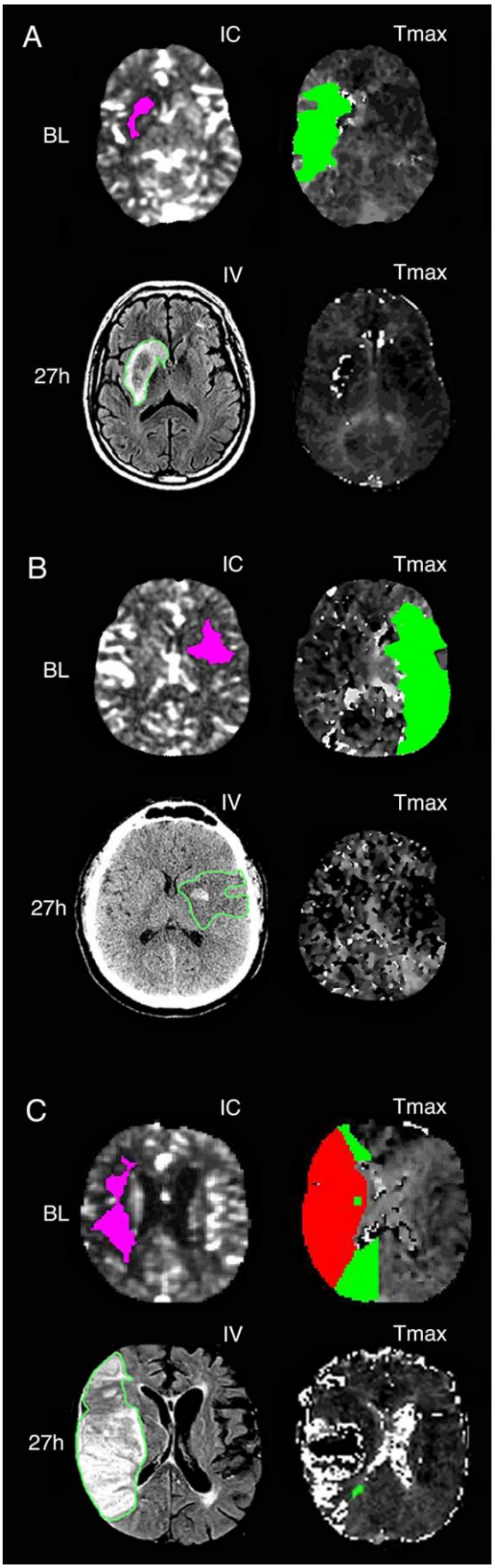
The primary finding of this study is that ischemic core volumes, identified primarily with CT perfusion, predicted 27-hour infarct volumes in patients who achieved reperfusion in both the endovascular and tPA-alone groups of SWIFT PRIME. In addition, baseline hypoperfusion volumes assessed with Tmax > 6-second volume strongly correlated with 27-hour infarct volumes in patients who did not reperfuse. An early estimate of the volume and location of ischemic core and potentially salvageable tissue may have a number of clinical benefits ranging from confirmation of the diagnosis of brain ischemia to determining optimal therapeutic interventions and predicting clinical and radiographic outcomes.

These finding are consequential because CT scanning is the primary imaging modality used for evaluation of patients with acute ischemic stroke and noncontrast CT scans have low sensitivity for identification of regions of early irreversible ischemic injury or tissue at risk of infarction. Considerable data from previous studies support DWI as the most accurate imaging sequence available for estimating the ischemic core in acute stroke

TABLE 3. Baseline and 24-Hour Ischemic Lesion Volumes in Patients with Reperfusion: Target Mismatch versus Malignant

Patients	Outcome								
	Median Baseline Core Volume: Both Groups, ml (IQR) [No.]	Median 24-Hour Infarct Volume: Both Groups, ml (IQR) [No.]	Absolute Volume Difference: Both Groups, ml (IQR) [No.]	Median Baseline Core Volume: tPA Alone, ml (IQR) [No.]	Median 24-Hour Infarct Volume: tPA Alone, ml (IQR) [No.]	Absolute Volume Difference: tPA Alone, ml (IQR) [No.]	Median Baseline Core Volume: Solitaire + IV tPA, ml (IQR) [No.]	Median 24-Hour Infarct Volume: Solitaire + IV tPA, ml (IQR) [No.]	Absolute Volume Difference: Solitaire + IV tPA, ml (IQR) [No.]
Patients who achieved TICI 2b–3 and TMM	3 (0–11) [51]	15.1 (5.7–39.1) [51]	11.1 (3.8–27.7) [51]	—	—	—	3 (0–11) [51]	15.1 (5.7–39.1) [51]	11.1 (3.8–27.7) [51]
Patients with > 90% reperfusion at 27 hours and TMM	2 (0–11) [63]	14.5 (5.7–34.1) [63]	9.2 (4–21.5) [63]	2.5 (2–17) [18]	14.2 (6.9–34.1) [18]	11 (5.9–21.5) [18]	2 (0–10) [45]	14.5 (5.7–31.6) [45]	9.1 (3.8–17.9) [45]
Patients with > 90% reperfusion at 27 hours and malignant	22 (18–27) [6]	83.2 (49.4–139.2) [6]	37.8 (22.4–93) [6]	22 (20–24) [2]	152.6 (36.2–269) [2]	130.6 (16.2–245) [2]	22.5 (17–65) [4]	83.2 (52.35–125.1) [4]	37.8 (29.3–66.15) [4]

IQR = interquartile range; IV = intravenous; TICI = Thrombolysis in Cerebral Infarction; TMM = target mismatch profile; tPA = tissue plasminogen activator.



patients.[21,22] The SWIFT PRIME study confirms the generally held perception that acute CT perfusion is much more widely available than urgent multimodal MRI scanning; sites were given the option to use either modality, yet MRI was performed at baseline in only a few centers. Therefore, SWIFT PRIME is not an optimal data set for confirming the accuracy of DWI for assessing infarct core, as only 14 patients with > 90% reperfusion were available in the data set. These 14 patients had a 17ml (IQR = 9–38) median difference between baseline DWI lesion volume and 27-hour infarct volume, which is generally comparable to prior larger studies that reported an approximately 10ml median difference between baseline DWI volumes and follow-up infarct volumes in patients with early reperfusion.[8]

SWIFT PRIME provided a very favorable patient population to evaluate the accuracy of a real time CT perfusion approach, with automated volumetric processing of ischemic core lesions, because the vast majority of patients had baseline CT perfusion and a high proportion of these patients achieved early reperfusion. The CBF threshold of a >70% reduction compared to normally perfused tissue used in this study for identification of ischemic core lesions on CT perfusion forecast the 27-hour infarct volume, in patients with reperfusion at 27 hours, with a median absolute error of 9ml for TMM patients, which is very similar to the accuracy of DWI reported in prior studies.

The same automated software program, RAPID, was installed at study sites and, in conjunction with a harmonized study protocol across study sites, provided an important benefit. Prior studies have documented substantial differences in ischemic core volumes generated by different processing programs from the same data set.[23,24] Fully automated processing also led to faster processing times; the median was 138 seconds for scanners with whole brain coverage and 234 seconds for scanners that obtained 2 separate 4cm-thick slabs. These results indicate that automated CT perfusion data processing can be performed rapidly on a wide variety of scanners.

FIGURE 4: Examples where 27-hour infarct volume is larger than predicted infarct volume. (A) The baseline (BL) core is 14ml (pink); following complete reperfusion, the 27-hour infarct volume is 45ml (green outline) and demonstrates hemorrhagic transformation. (B) The baseline core is 10ml (pink); following complete reperfusion, the 27-hour infarct volume (green outline) is 47ml and has hemorrhagic transformation. (C) Example of the malignant profile. The baseline core is 24ml (pink) and the Tmax > 10-second volume (shown in red) is 177ml. Following 98% reperfusion, the 27-hour infarct volume (green outline) is 269ml. IC = ischemic core; IV = infarct volume.

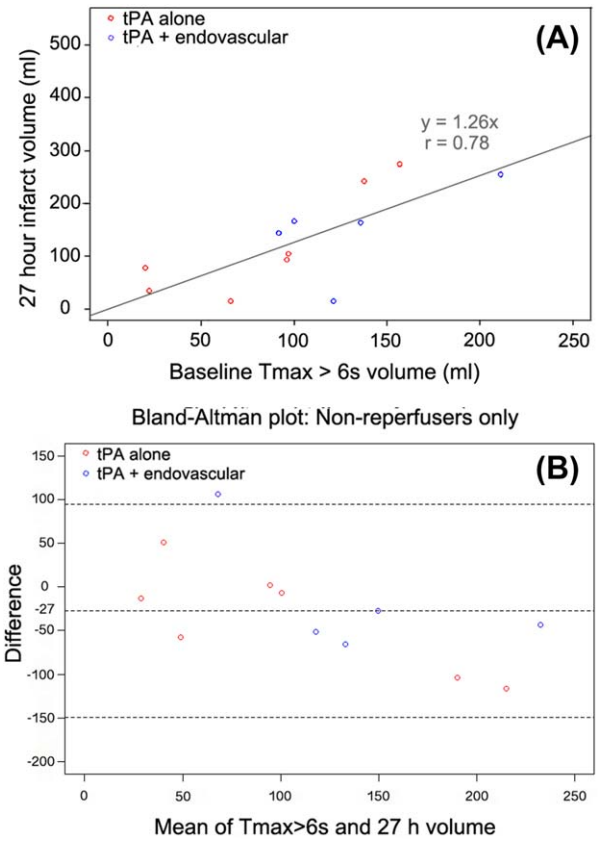


FIGURE 5: Scatter plot (A) and Bland–Altman plot (B) comparing the baseline Tmax > 6-second volume with the actual 27-hour infarct volume in patients with <10% reperfusion/ Thrombolysis in Cerebral Infarction = 0–1. For the Bland–Altman plot, the y-axis represents the baseline Tmax > 6-second volume − 27-hour infarct volume; therefore, negative values indicate that the 27-hour volume is larger than the baseline Tmax > 6-second volume. For the Bland–Altman plot, the bias is −27.3ml (95% confidence interval = −66.8 to 12.2). tPA = tissue plasminogen activator.

Overestimation of Ischemic Core Lesions

Eleven percent of all patients had 27-hour infarct volumes that were smaller than the pretreatment ischemic core lesion volumes (the median difference in these patients was 4ml). In these patients, the baseline ischemic core appears to have been slightly overestimated. Although not observed in the SWIFT PRIME cohort (see Fig 3), substantial overestimation would be clinically important because techniques that overestimate ischemic core tissue could lead to erroneous decisions to withhold a potentially efficacious therapy. Of note, the baseline ischemic core volumes in SWIFT PRIME were typically small, which limits the potential to identify core overestimation. In a study of 103 acute stroke patients who underwent DWI immediately after CT perfusion, which included patients with substantially larger core volumes, the specificity of CT perfusion for predicting a DWI lesion exceeding 50ml was 99%.[19] This study used the same software and postprocessing thresholds as SWIFT PRIME. Therefore, it appears unlikely that overestimation of ischemic core volume would unnecessarily exclude patients from reperfusion therapy using the RAPID algorithm with the >70% reduction in CBF threshold; however, additional research that includes patients treated at earlier time points and with larger ischemic core lesions is required to further clarify this issue.

Underestimation of Ischemic Core Lesions

In general, despite > 90% reperfusion, the estimated volume of ischemic core tissue at baseline was typically smaller than the 27-hour infarct volume (median difference in reperfused patients with "underestimation of core" by CT perfusion was 15ml). There are a number of potential explanations for why baseline ischemic core lesions may be smaller than the 27-hour infarct volumes. Previous studies have shown that infarct volumes increase

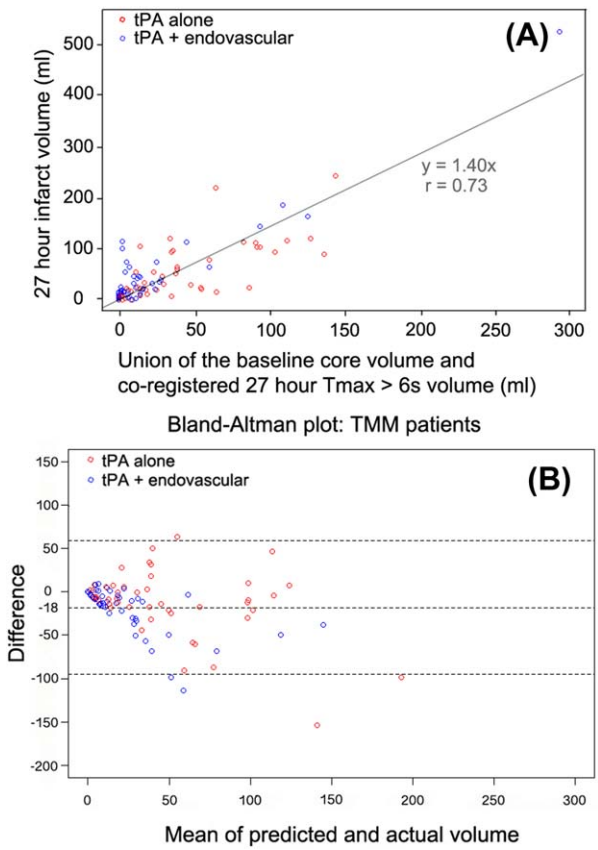


FIGURE 6: Scatter plot (A) and Bland–Altman plot (B) comparing the union of baseline ischemic core volume and the 27-hour Tmax > 6-second volume (predicted 27-hour volume) with the actual 27-hour infarct volume in target mismatch patients. For the Bland–Altman plot, the y-axis represents the predicted infarct volume − actual 27-hour infarct volume; therefore, negative values indicate that the 27-hour volume is larger than the predicted volume. For the Bland–Altman plot, the bias is −18.1ml (95% confidence interval = −25.9 to −10.3). TMM = target mismatch profile; tPA = tissue plasminogen activator.

steadily for about 3 days after symptom onset and then decrease slowly due to resolution of vasogenic edema.[25] Evidence of edema with associated mass effect at the time of the 27-hour scan was not unusual in SWIFT PRIME (see Fig 4). Therefore, it is likely that the volumetric differences between early ischemic core and final infarct were overestimated because of early edema in some patients.

Other potential explanations for apparent underestimation of ischemic core include incomplete or delayed reperfusion and growth of the ischemic core between imaging and reperfusion as well as reperfusion injury (which may result in hemorrhagic transformation of the ischemic core lesion). Data supportive of these potential explanations include the finding that the median difference between observed and expected volumes was smaller in endovascularly treated patients who were reperfused more completely; TMM patients who achieved TICI = 3 reperfusion in the catheterization laboratory had a median difference between baseline core and 27-hour infarct volume of only 9ml versus 29ml for patients with TICI = 2b reperfusion. Furthermore, in the multivariate analysis, achieving TICI = 3 reperfusion was associated with greater accuracy for predicting the 27-hour infarct volume. In addition, patients with the malignant profile who reperfused had substantially larger differences between baseline ischemic core and 27-hour infarct volumes than the TMM patients. This finding confirms prior data indicating that patients with the malignant profile experience more rapid early infarct growth than patients with the TMM profile. Taken together, these data support the assertion that infarct growth between imaging and reperfusion, as well as the degree of reperfusion obtained, likely contributes to the differences been the baseline ischemic core volume and the 27-hour infarct volumes.

In addition to growth prior to reperfusion, hemorrhagic transformation of reperfused ischemic core tissue clearly accounts for some of the difference between expected and observed 27-hour volumes. PH was significantly associated with decreased accuracy of prediction of 27-hour infarct volume in the multivariate model. Furthermore, HI of the ischemic core lesion (see Fig 4A, B) occurred in the majority of patients with "core underestimation" in Part 1 of the study. An additional potential explanation for underestimation is the possibility that CBF volumes may not accurately identify ischemic core lesions in some patients.

Interestingly, patients who achieved >90% reperfusion had similar median 27-hour infarct volumes irrespective of treatment group (18ml in the tPA group vs 16ml in the tPA + Solitaire group). The precise time when reperfusion occurred is unknown in the tPA group; however, since infarct volumes were comparable to the rapidly reperfused endovascular group, we suspect that when reperfusion occurred, it typically also occurred early in tPA patients. However, > 90% reperfusion was achieved more than twice as often in the endovascular group, which likely accounts for the dramatic differences in favorable clinical outcomes (modified Rankin Scale = 0–2 at 90 days) achieved in the full study population (60.2% vs 35.5%, $p < 0.001$).

Prediction of Critically Hypoperfused Tissue

SWIFT PRIME is not an ideal database for assessing the ability of baseline perfusion imaging parameters to predict subsequent infarct volumes in patients who do not reperfuse because very few patients in either treatment group failed to have at least partial reperfusion at 27 hours. The 12 patients who had < 10% reperfusion/TICI = 0–1 had infarct volumes that were >100ml larger than patients who achieved reperfusion. Among these 12 nonreperfusers, the Tmax > 6-second volume at baseline correlated significantly with 27-hour infarct volumes, but an accurate assessment of the quantitative relationship between baseline Tmax > 6-second volume and final infarct volume is not possible with this small data set. Twenty-seven–hour infarct volumes were substantially smaller than anticipated in 2 patients. One of these was a tPA-only patient who had evidence of continued infarct growth beyond 27 hours. The other was a Solitaire-treated patient who did not have a 27-hour perfusion scan to clarify whether reperfusion occurred after the end of the procedure. An additional limitation for this analysis is that full brain coverage was not obtained at baseline on most of the CT perfusion studies; therefore, the full extent of baseline Tmax > 6-second lesions was underestimated in some patients.

Prediction of 27-Hour Infarct Volumes from Baseline Core and 27-Hour Tmax > 6-Second Volumes

Prediction of infarct volumes for the full population of patients requires knowledge of the volume of irreversibly injured ischemic core tissue at baseline as well as the volume of tissue that remains critically hypoperfused after treatment. This was assessed in all patients who met the study's imaging criteria (TMM patients) and had both baseline core and 27-hour follow-up perfusion imaging. Among these TMM patients, the union of baseline core and 27-hour follow-up Tmax > 6-second hypoperfusion volume predicted the 27-hour infarct volume with a median absolute difference of 13ml. For patients with baseline CT perfusion the result was 11ml, which is comparable to the median 15ml difference noted in a similar analysis from the entirely MRI-based DEFUSE 2 study.[8]

Of note, some of the patients who did not reperfuse had 27-hour infarct volumes that were smaller than predicted. Prior studies have demonstrated that infarcts often continue to expand for at least 2 to 3 days in patients who do not reperfuse versus typically <24 hours in patients with early reperfusion.[25,26] These results are compatible with the anecdotal results described from the subsequent unscheduled scans obtained in SWIFT PRIME patients that documented continued infarct growth beyond 27 hours. Therefore, it appears likely that many of these "nonreperfusers" would have actual infarct volumes that more closely approximate the predicted volume if the "final infarct volume" had been assessed at a later time point. Because the majority of nonreperfusion patients were in the tPA group, this provides a potential bias toward underestimating treatment effect of endovascular therapy for reducing final infarct volume if infarct volumes are assessed at early time points (nonreperfused patients, who are primarily in the medical therapy groups, are more likely to have infarct volumes underestimated).

Limitations

This study has a number of limitations. Reperfusion and infarct volumes are not stationary measures because arterial obstructions, perfusion deficits, and ischemic parenchymal lesions can evolve independently in both the early hours after stroke onset and following therapeutic interventions. This study provides data at only 2 snapshots in time. Twenty-seven hours is not likely to be the optimal time to assess final infarct volume, as the ultimate infarct volume may be overestimated because of edema and hemorrhage or underestimated because the ischemic lesion is still evolving. The baseline core volumes in SWIFT PRIME were typically small (median = 6ml), and the baseline scans were performed very early after symptom onset. These results may not apply to patients with larger baseline core volumes, those scanned at later time points, or those analyzed with different postprocessing software. Only a subset of patients had 27-hour perfusion images, so the extent of reperfusion is not available for the full sample size. Very few patients had limited or no reperfusion, so the predictions of infarct volumes in nonreperfused patients are less precise.

The results of this study support the conclusion that baseline ischemic core volumes on both CT perfusion and MRI approximate the eventual infarct volumes in patients who achieve early reperfusion. In addition, among target mismatch patients, the union of baseline core and early follow-up hypoperfusion volume accurately predicts infarct volume in the majority of patients. These results support the premise that advanced imaging has the potential to play an important role for both patient selection and monitoring of the therapeutic response to acute stroke interventions.

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Authorship

All authors participated in study design, data collection, and critical review and revision of the manuscript. G.W.A. drafted the manuscript.

Potential Conflicts of Interest

G.W.A.: personal fees, Covidien, iSchemaView, Lundbeck; equity interest, iSchemaView; patent, U.S. 8,837,800 (related to RAPID software). M.G.: personal fees, grant, Covidien; patent, Systems and Methods for Diagnosing Strokes (licensed to GE Healthcare). R.J.: personal fees, Covidien; employer University of California holds patent on retriever devices for stroke. A.B.: personal fees, Covidien. H.-C.D.: personal fees, Covidien, Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, Mindframe, Neurobiological Technologies, Novartis, Novo Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, Yamanouchi; funding, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi-Aventis, Syngis, Talecris, Lundbeck, German Research Council, German Ministry of Education and Research, European Union, NIH, Bertelsmann Foundation, Heinz-Nixdorf Foundation; editor, *Aktuelle Neurologie, Arzneimitteltherapie, Kopfschmerznews, Stroke News, Treatment Guidelines of the German Neurological Society*; coeditor, *Cephalalgia*; editorial board, *Lancet Neurology, Stroke, European Neurology, Cerebrovascular Disorders*. E.I.L.: personal fees, Covidien, Abbott, Renders Medical/Legal Opinion; shareholder/ownership, Intratech Medical, Blockade Medical. V.M.P.: personal fees, Covidien. C.C.: personal fees, Covidien, Codman, Stryker, Sequent Medical, Microvention. D.J.C.: personal fees, Covidien, Medtronic, Abbott Vascular; grants, Covidien, Medtronic, Boston Scientific, Abbott Vascular. W.H.: personal fees, Covidien. O.J.: personal fees, Covidien. T.D.J.: nonfinancial support,

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