Large Volumes of Critically Hypoperfused Penumbral Tissue Do Not Preclude Good Outcomes After Complete Endovascular Reperfusion

Redefining Malignant Profile

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Background and Purpose—Acute ischemic stroke patients with large volumes of severe hypoperfusion (T_{max}>10 s>100 mL) on magnetic resonance imaging have a higher likelihood of intracranial hemorrhage and poor outcomes after reperfusion. We aim to evaluate the impact of the extent of T_{max}>10 s CTP lesions in patients undergoing successful treatment.

Methods—Retrospective database review of endovascular acute ischemic stroke treatment between September 2010 and March 2015 for patients with anterior circulation occlusions with baseline RAPID CTP and full reperfusion (mTICI 3). The primary outcome was the impact of the T_{max}>10 s lesion spectrum on infarct growth. Secondary safety and efficacy outcomes included parenchymal hematomas and good clinical outcomes (90-day modified Rankin Scale score, 0–2).

Results—Of 684 treated patients, 113 patients fit the inclusion criteria. T_{max}>10 s>100 mL patients (n=37) had significantly higher baseline National Institutes of Health Stroke Scale (20.7±3.8 versus 17.0±5.9; P<0.01), more internal carotid artery terminus occlusions (29% versus 9%; P=0.02), and larger baseline (38.6±29.6 versus 11.7±15.8 mL; P<0.01) and final (60.7±60.0 versus 29.4±33.9 mL; P<0.01) infarct volumes when compared with patients without T_{max}>10 s >100 mL (n=76); however, the 2 groups were otherwise well balanced. There were no significant differences in infarct growth (22.1±51.6 versus 17.8±32.4 mL; P=0.78), severe intracranial hemorrhage (PH2: 2% versus 4%; P=0.73), good outcomes (90-day mRS score, 0–2: 56% versus 59%; P=0.83), or 90-day mortality (16% versus 7%; P=0.28). On multivariate analysis, only baseline National Institutes of Health Stroke Scale (odds ratio, 1.19; 95% confidence interval, 1.06–1.34; P<0.01) and baseline infarct core volume (odds ratio, 1.05; 95% confidence interval, 1.02–1.08; P<0.01) were independently associated with T_{max}>10 s>100 mL. There was no association between T_{max}>10 s>100 mL with any PH, good outcome, or infarct growth.

Conclusions—In the setting of limited baseline ischemic cores, large T_{max}>10 s lesions on computed tomographic perfusion do not seem to be associated with a higher risk of parenchymal hematomas and do not preclude good outcomes in patients undergoing endovascular reperfusion with contemporary technology. **(*Stroke*. 2016;47:94-98. DOI: 10.1161/STROKEAHA.115.011360.)**

Key Words: computed tomography, x-ray ■ magnetic resonance imaging ■ perfusion imaging ■ reperfusion ■ stroke

Reperfusion therapy remains the mainstay of acute ischemic stroke treatment but its clinical benefit comes at the cost of potential harm from reperfusion injury leading to cerebral edema and hemorrhagic complications. Advanced computed tomography (CT) and magnetic resonance imaging (MRI) techniques have emerged as promising tools to improve treatment selection by excluding patients who are particularly prone to harm and have low chances of benefit. The term Malignant profile was originally proposed by the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study (DEFUSE) investigators to describe imaging patterns of severe cerebral ischemia associated with high likelihood of symptomatic intracranial hemorrhage (SICH) or poor outcome after reperfusion in acute ischemic stroke and was empirically defined as a baseline lesion on diffusion-weighted MRI (DWI) >100 mL or a lesion on

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perfusion-weighted imaging of >100 mL using T_{max} delay of >8 s.[1] In the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) study, patients with the malignant profile were also found to have greater infarct growth and lower frequency of reperfusion.[2] The DEFUSE–EPITHET Pooled analysis subsequently confirmed higher rates of parenchymal hematomas and poor outcomes in malignant profile patients who experienced reperfusion versus no reperfusion while also suggesting a smaller T_{max}>8 s lesion (>85 mL) as the optimal definition for the malignant profile.[3]

The DEFUSE group also introduced the concept of the Target Mismatch (TMM) profile to describe patients who would presumably be ideal candidates for reperfusion therapy. In the DEFUSE-2 trial, TMM on MRI was defined by (1) a ratio between the hypoperfused tissue (on T_{max}>6 s maps) and ischemic core on DWI maps of ≥1.8, with an absolute difference of ≥15 mL; (2) DWI ischemic core volumes ≤70 mL; and (3) volume of tissue with severe hypoperfusion (T_{max}>10 s) of ≤100 mL.[4] In comparison with non-TMM patients, TMM patients have been found to have lower rates of infarct growth and better outcomes after intravenous thrombolysis or endovascular therapy.[2,5] However, the data supporting the assumption that perfusion imaging using the T_{max}>10 s threshold can reliably identify brain tissue with severe enough hypoperfusion to lead to cell death was derived from studies using intravenous recombinant tissue-type plasminogen activator (r-tPA) or endovascular treatment that predates the stent retriever technology, which is known to result in faster and better reperfusion when compared with both intravenous r-tPA and the previous thrombectomy devices.[6–11] The aim of this study was to evaluate the impact of the Malignant Profile CT perfusion component T_{max}>10 s>100 mL lesion on the outcomes of patients undergoing complete reperfusion with contemporary technology.

Methods

Patient Selection

This was a review of the prospectively collected interventional database from a tertiary care academic institution for consecutive cases of endovascular acute ischemic stroke treatment between October 2010 and March 2015 with (1) anterior circulation intracranial large-vessel occlusions involving the intracranial internal carotid artery and proximal middle cerebral artery M1 and M2 segments that (2) underwent pretreatment CT perfusion (CTP) resulting adequate postprocessing perfusion maps, and (3) achieved full reperfusion (defined as modified treatment in cerebral ischemia [mTICI] grade 3). This study was approved by the local institutional review board.

Imaging Protocols

Imaging Acquisition

The study patients underwent an institutional stroke imaging protocol, including noncontrast CT, CT angiogram, and CTP. CT was performed on a 40-mm, 64-detector row clinical system (LightSpeed VCT; GE Healthcare, Milwaukee, WI). Helical noncontrast CT (120 kV; 100–350 auto-mA; CT dose index, ≈43.15) was performed from the foramen magnum through the vertex at a 5.0-mm section thickness. In the absence of visible intracranial hemorrhage during real-time evaluation by vascular neurologist, 2 contiguous CTP slabs were obtained for 8-cm combined coverage of the supratentorial brain, obtained at eight 5-mm sections per slab. Cine mode acquisition (80 kV; 100 mA; CT dose index, ≈293.48) permitting high-temporal resolution (1-s sampling interval) dynamic bolus passage imaging was obtained after the administration of 35-mL iodinated contrast (iopamidol, Isovue 370; Bracco, Princeton, NJ) power injected at 5 mL/s through an 18-ga or larger antecubital intravenous access. Contrast administration was followed by a 25-mL saline flush at the same rate. Finally, helical CT angiogram (120 kV; 200–350 auto-mA; CT dose index, ≈38.08) was performed from the carina to the vertex (section thickness/interval, 0.625/0.375 mm) after intravenous administration of 70-mL iodinated contrast injected at 5 mL/s and followed by a 25-mL saline flush.

Image Processing and Perfusion Lesion Definitions

Images were processed with a fully automated, commercially available CT Perfusion software (RAPID version 4.5.0. iSchemaView Inc., Menlo Park, CA) to identify potentially salvageable brain tissue as previously described.[9,12,13] Brain tissue at risk of infarction (ischemic penumbra) was distinguished from mildly hypoperfused brain by a delay for the maximum of the tissue residue function longer than 6 s (T_{max}>6 s). Irreversibly injured tissue (ischemic core) was defined by reduction in the relative cerebral blood flow to <30% of that in normal tissue.[9] A Malignant Profile perfusion lesion was defined by >100 cc delay for the maximum of the tissue residue function longer than 10 s (T_{max}>10 s>100 mL).[4] Fourteen patients with nondiagnostic CTP scans due to motion artifact or suboptimal contrast bolus that did not allow for accurate RAPID-generated volumetric maps were excluded. In addition, 5 patients with technically inadequate follow-up scans because of severe motion artifact or uneven slices that would compromise volumetric analysis were excluded.

Follow-up in all patients included MRI documenting final infarct volumes before hospital discharge. Final infarct volumes were defined preferentially by MRI, which was performed in 97 (86%) patients. Noncontrast CT was performed if there was a contraindication to MRI (eg, pacemaker and clinical instability). All studies were performed within the first 5 days of the treatment. DWI sequence was preferentially used if MRI was obtained within the first 72 hours of the stroke and fluid-attenuated inversion recovery sequence if the MRI was performed between 3 and 5 days. For noncontrast CT, window/level settings were adjusted to maximize contrast between the normal and infarcted brain. In cases with significant cerebral edema, volume increases from swelling were accounted for by excluding infarcted tissue that extended across midline or produced ventricular effacement (compared with pretreatment ventricular configuration). Edema producing sulcal effacement was not excluded. If present, hemorrhagic changes were incorporated in the final infarct volumes. Final infarct volumes were measured after export of raw Digital Imaging and Communications in Medicine (DICOM) data to the Fiji release of the ImageJ software platform (http://imagej.nih.gov/ij/).[14]

Statistical Analysis and Outcome Measures

Parametric continuous variables are reported as mean±SD. Categorical variables are reported as proportions. Since dichotomization may reduce the measured strength of association because of loss of information, univariate linear regression analysis was performed using T_{max}>10 s volume as a continuous variable to enhance statistical power.[15] Infarct growth was defined as the difference of final infarct volume minus baseline ischemic core volume (relative cerebral blood flow <30% normal brain). The primary outcome variable was the impact of the T_{max}>10 s lesion spectrum on infarct growth. Secondary safety and efficacy outcomes included parenchymal hematomas and good clinical outcomes (90-day modified Rankin Scale, 0–2). Sensitivity analysis was performed dichotomizing T_{max}>10 s using threshold of 100 mL (eg, Malignant Profile perfusion lesion). Between groups, comparisons for continuous/ordinal variables were made with Student *t* test/Mann–Whitney *U* test. Categorical variables were compared by χ^2/Fisher exact test. Correlation coefficient was calculated with Pearson's ρ. Significance was set at P<0.05. Multivariate linear and logistic (variable selection method) regression analyses were performed for variables <0.10 level of significance. Statistical analyses were performed using SPSS Statistics 21 (IBM, Armonk, NY).

Results

Of 684 patients treated within the study period, 113 patients fit inclusion criteria (eg, mTICI 3 reperfusion of a proximal anterior circulation occlusion after technically successful CT perfusion acquisition and processing) and were included in the current analysis. Overall baseline characteristics, procedural, radiological, and outcome data are displayed in Table 1. The mean baseline stroke core volume was 20.1±41.3 mL and final infarct volume was 39.2±45.8 mL, resulting in mean infarct growth volume of 19.1±41.3 mL. The mean T_{max}>10 s lesion volume for the whole cohort was 89.9±89.2 mL. Linear (eg, continuous T_{max}>10 s lesion volume) and logistic (eg, T_{max}>10 s lesion volume dichotomized at >100 cc) univariate and multivariate regression analyses for factors predictive of larger T_{max}>10 s lesions yielded similar results (Tables 1 and 2).

Patients with and without Malignant Profile perfusion lesions (eg, T_{max}>10 s>100 mL) had similar ages, times from CTP to TICI 3 reperfusion, types of procedural sedation, and rates of intravenous r-tPA and stent retriever usage. On univariate analysis, patients with Malignant Profile perfusion lesions (n=37) had significantly higher baseline National Institutes of Health Stroke Scale (20.7±3.8 versus 17.0±5.9; P<0.01), higher frequency of internal carotid artery terminus occlusions (29% versus 9%; P=0.02), and larger baseline (38.6±29.6 versus 11.7±15.8 mL; P<0.01) and final (60.7±60.0 versus 29.4±33.9 mL, P<0.01) infarct core volumes when compared

Table 1. Univariate Linear Analyses of T_{max}>10 s as a Continuous Variable (Linear Regression) and Univariate Logistic Analyses of T_{max}>10 s Dichotomized at ≤100 Versus >100 cc (eg, Malignant Profile Perfusion Lesion)

	Overall, n=113	*P* Value Linear Regression	T_{max}>10 s ≤100 cc, n=76	T_{max}>10 s>100 cc, n=37	*P* Value Logistic Regression
Baseline					
Age	63.9±15.2	0.29	64.7±15.8	62.1±13.8	0.37
Hypertension	81 (71%)	0.55	51 (67%)	30 (81%)	0.18
Dyslipidemia	43 (38%)	0.39	25 (33%)	18 (48%)	0.14
Atrial fibrillation	44 (39%)	0.14	35 (46%)	9 (24%)	0.03*
Diabetes mellitus	20 (17%)	0.83	11 (14%)	9 (24%)	0.20
Intravenous tPA	53 (47%)	0.60	37 (48%)	16 (43%)	0.68
NIHSS	18.2±5.6	<0.01*	17.0±5.9	20.7±3.8	<0.01*
Mean arterial pressure, mm Hg	99.1±19.4	0.68	99.1±19.8	99.0±18.9	0.97
Intracranial occlusion site					
ICA-T	18 (16%)	0.02*	7 (9%)	11 (29%)	0.01*
MCA M1	69 (61%)	0.36	48 (63%)	21 (56%)	0.54
MCA M2	25 (22%)	0.73	19 (25%)	6 (16%)	0.34
Procedure					
General anesthesia	21 (18%)	0.18	13 (17%)	8 (21%)	0.60
Stent retriever	95 (84%)	0.20	63 (83%)	32 (86%)	0.78
Time from stroke onset to groin puncture, min	425±314	0.12	357±246	457±339	0.12
Time from CT initiation to TICI-3 reperfusion, min	124±52	0.55	124±52	124±52	0.99
CT perfusion					
CBF core, mL	20.1±41.3	<0.01*	11.7±15.8	38.6±29.6	<0.01*
Final infarct, mL	39.2±45.8	<0.01*	29.4±33.9	60.7±60.0	<0.01*
Infarct growth, mL	19.1±41.3	0.78	17.8±32.4	22.1±51.6	0.75
Outcomes					
Hemorrhage					
Parenchymal hematoma 1	7 (6%)	0.41	3 (4%)	4 (11%)	0.21
Parenchymal hematoma 2	4 (3%)	0.51	3 (4%)	1 (2%)	0.73
Subarachnoid hemorrhage	3 (2%)	0.49	2 (2%)	1 (2%)	0.99
mRS score 0–2 at 90 days	58/100 (58%)†	0.81	40/68 (59%)‡	18/32 (56%)	0.83
Death at 90 days	10/100 (10%)†	0.64	5/68 (7%)‡	5/32 (16%)	0.28

CBF indicates cerebral blood flow; CT, computed tomography; ICA-T, internal carotid artery terminus; IV tPA, intravenous tissue-type plasminogen activator; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hemorrhage; and tPA, tissue-type plasminogen activator.

*P<0.05.

†n=100.

‡n=68.

Table 2. Multivariate Linear Analyses of T_{max}>10 s as a Continuous Variable (Linear Regression) and Multivariate Logistic Analyses of T_{max}>10 s Dichotomized at ≤100 Versus >100 cc (eg, Malignant Profile Perfusion Lesion)

	Multivariate Linear Regression			Multivariate Logistic Regression		
	Standarized β	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Atrial fibrillation	…	…	…	0.38	0.12 to 1.22	0.10
NIHSS	0.23	0.95 to 6.34	<0.01*	1.19	1.06 to 1.34	<0.01*
ICA-T occlusion	0.73	–27.02 to 58.94	0.46	2.86	0.75 to 10.8	0.12
Baseline core (CBF)	0.38	0.78 to 2.04	<0.01*	1.05	1.02 to 1.08	<0.01*

CBF indicates cerebral blood flow; ICA-T, internal carotid artery terminus; and NIHSS, National Institutes of Health Stroke Scale.

*P<0.05.

with patients without Malignant Profile perfusion lesions (n=76). However, there were no significant differences in the absolute volumes of infarct growth (22.1±51.6 versus 17.8±32.4 mL; P=0.78), severe intracranial hemorrhage (PH2: 2% versus 4%; P=0.73), good outcomes (90-day mRS score, 0–2: 56% versus 59%; P=0.83), or 90-day mortality (16% versus 7%, P=0.28) among patients with and without Malignant Profile perfusion lesion.

On multivariate analysis, only baseline National Institutes of Health Stroke Scale (odds ratio, 1.19; 95% confidence interval [CI], 1.06–1.34; P<0.01) and baseline infarct core volume (odds ratio, 1.05; 95% CI, 1.02–1.08; P<0.01) were independently associated with Malignant Profile perfusion lesion (T_{max}>10 s>100 mL). Notably, T_{max}>10 s>100 mL lesion was not associated with any parenchymal hematoma (odds ratio, 1.32; 95% CI, 0.15–12.16; P=0.78), 90-day good outcome (odds ratio, 1.00; 95% CI, 0.99–1.01; P=0.17), or infarct growth (standardized β, –0.002; 95% CI, –0.008 to 0.006; P=0.74) after being forced into the regression models (Tables I–III in the online-only Data Supplement).

Discussion

Our study demonstrates that in the era of modern thrombectomy technology, and as long as fast and complete reperfusion is achieved, the finding of large T_{max}>10 s lesions alone does not seem to have any meaningful prognostic importance. Specifically, in the absence of large baseline ischemic cores, larger T_{max}>10 s lesions on CT perfusion are not associated with higher rates of infarct growth, severe intracranial hemorrhage (eg, PH1, PH2, or SAH), unfavorable outcomes, or mortality. Therefore, large T_{max}>10 s lesion volumes in isolation (eg, without large overlapping areas of ischemic core on DWI or CTP relative cerebral blood flow <30% maps) should not be considered an exclusion criterion for endovascular reperfusion therapy and the definitions of TMM and Malignant Profile should be revised to reflect these findings.

In our cohort of patients, larger T_{max}>10 s volumes were directly associated with higher baseline National Institutes of Health Stroke Scale and larger baseline infarct core volumes presumably because T_{max}>10 s is a perfusion imaging surrogate for poor collateral flow given that worse collateral flow will lead to greater delay in contrast arrival. Tissue fate in such patients is likely to be highly dependent on time and extent of reperfusion. Because good collateral flow is independently associated with higher rates of reperfusion, smaller final infarct sizes, lower rates of SICH, and better clinical outcomes after endovascular therapy,[16,17] we think that the previously described associations between large T_{max}>10 s lesion volumes and worse outcomes do exist but are likely dependent both on the time from imaging to reperfusion and on the final degree of reperfusion.

In contrast to the current study where less than half of the patients received intravenous r-tPA, all DEFUSE and Extending the Time for Thrombolysis in Emergency Neurological Deficits With Intra-Arterial (EXTEND-IA) therapy[1,2] patients underwent intravenous thrombolysis. This greater exposure to systemic r-tPA may have made their patients with T_{max}>10 s >100 mL more prone to SICH and poor outcomes because larger T_{max}>10 s lesions are associated with larger baseline infarct cores, which are known to have a higher risk of hemorrhagic transformation after intravenous r-tPA.[18] As suggested by the recent thrombectomy trials, it is also possible that the reperfusion post intravenous thrombolysis in the DEFUSE and EPITHET trials was delayed and less complete in comparison with the endovascular technology used in our study. Faster and more complete reperfusion along with the lower exposure to intravenous r-tPA (47% versus 100%) seen in our study could explain the differences of the impact of large T_{max}>10 s lesions on infarct growth, SICH, and clinical outcomes in our analyses versus the DEFUSE and EXTEND-IA trials.

Similarly, DEFUSE-2 used older endovascular technology known to be inferior to the current standards in terms of both speed and completeness of reperfusion. Indeed, only 18% of the DEFUSE-2 patients achieved full (TICI 3) reperfusion at the end of the treatment.[19] Moreover, for their study purposes, reperfusion was defined as a >50% reduction in the volume of the perfusion-weighted imaging (T_{max}>6 s) lesion between the baseline and the early follow-up MRI (obtained within 12–18 hours after the endovascular procedure) or as >50% angiographic reperfusion of the territory supplied by the occluded vessel at completion of the endovascular procedure if MRI data were not available. The inclusion of patients with incomplete and delayed reperfusion in their analysis may have confounded their results and overestimated the deleterious effects of the Malignant Profile perfusion lesion (T_{max}>10 s >100 mL). In contrast, in the current study, we only included patients with full (TICI 3) reperfusion as the inclusion of any patients with suboptimal reperfusion could have led to larger final infarct volumes because of the lack of reperfusion itself

(areas of T_{max}>10 s lesions are expected to progress to dead brain in the absence of reperfusion) as opposed to because of the variable in question, for example, the effect of severe hypoperfusion (T_{max}>10 s lesion) on pretreatment CT perfusion imaging.

Our findings are of substantial importance. As the rates of optimal reperfusion (mTICI 2b-3) are now in the 70% to 90% range,[6–11] optimizing patient selection became increasingly important in the quest to further improve patient outcomes. However, it is critical that these selection techniques do not exclude patients, who could potentially benefit from reperfusion, as it was done in the SWIFT Prime trial, which excluded CTP-selected patients with the Malignant Profile perfusion lesion (T_{max}>10 s>100 mL). Our study has the limitations inherent to its retrospective methodology and its relatively small sample size. Moreover, the Malignant Profile perfusion lesion was validated in studies using MRI as opposed to CT perfusion. However, it has been demonstrated that a good correlation exists for CT and MRI T_{max} thresholds.[12] Furthermore, CTP is not only more frequently available but also faster than MRI selection making our findings more relevant to future patient selection paradigms.[13]

In conclusion, in the setting of limited baseline ischemic cores, large T_{max}>10 s lesion volumes on CT perfusion do not seem to be associated with a higher risk of clinically relevant ICH and does not preclude good outcomes in patients achieving successful endovascular reperfusion with the contemporary technology. Thus large T_{max}>10 s penumbral lesion volumes in isolation should not be used to exclude patients from endovascular therapy. Whether these findings are applicable to patients selected with MRI perfusion still require additional investigation.

Disclosures

Dr Nogueira: Stryker-Neurovascular (Trevo-2&DAWN/Trial PI), Covidien (SWIFT&SWIFT-PRIME/Steering-Committee, STARTrial/Core-Laboratory), Penumbra (3-D Separator Trial/Executive-Committee). The other authors report no conflicts.

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SUPPLEMENTAL MATERIAL

Table I: Multivariate logistic analyses of predictors of any parenchymal hemomatoma (PH-1 or PH-2):

	OR	**95%CI**	**p-Value**
mRS0-2 at 90 days	0.13	0.02-0.80	0.02
Mean Arterial Pressure	0.97	0.93-1.02	0.27
CTP to End of Procedure (min)	0.99	0.96-1.01	0.33
Ischemic Core Volume	1	0.98-1.03	0.62

Table II: Multivariate logistic analyses of predictors of good outcomes (90-day mRS 0-2):

	OR	**95%CI**	**p-Value**
Age	0.92	0.87-0.96	<0.01
NIHSS	0.83	0.74-0.93	<0.01
Final Infarct Volume	0.98	0.97-0.99	0.01
Any Parenchymal Hemorrhage	0.24	0.27-2.14	0.20
Hypertension	0.56	0.16-1.97	0.36

Table III: Multivariate linear regression analyses of infarct growth:

	Standarized beta	**95%CI**	**p-Value**
Final Infarct Volume	0.85	0.69—0.90	<0.01
Atrial Fibrillation	0.17	5.66—24.79	<0.01
NIHSS	-0.09	-1.60—0.19	0.12
mRS0-2 at 90 days	-0.40	-13.71—9.06	0.20
Mortality at 90 days	0.01	-14.5—19.12	0.78