T_{max} Volumes Predict Final Infarct Size and Functional Outcome in Ischemic Stroke Patients Receiving Endovascular Treatment

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Objective: The objective of this paper was to explore the utility of time to maximum concentration (T_{max})-based target mismatch on computed tomography perfusion (CTP) in predicting radiological and clinical outcomes in patients with acute ischemic stroke (AIS) with anterior circulation large vessel occlusion (LVO) selected for endovascular treatment (EVT).

Methods: Patients with AIS underwent CTP within 24 hours from onset followed by EVT. Critically hypoperfused tissue and ischemic core volumes were automatically calculated using T_{max} thresholds >9.5 seconds and >16 seconds, respectively. The difference between $T_{max} > 9.5$ seconds and $T_{max} > 16$ seconds volumes and the ratio between $T_{max} > 9.5$ seconds and $T_{max} > 16$ seconds volumes were considered ischemic penumbra and T_{max} mismatch ratio, respectively. Final infarct volume (FIV) was measured on follow-up non-contrast computed tomography (CT) at 24 hours. Favorable clinical outcome was defined as 90-day modified Rankin Scale 0 to 2. Predictors of FIV and outcome were assessed with multivariable logistic regression. Optimal T_{max} volumes for identification of good outcome was defined using receiver operating curves.

Results: A total of 393 patients were included, of whom 298 (75.8%) achieved successful recanalization and 258 (65.5%) achieved good outcome. In multivariable analyses, all T_{max} parameters were independent predictors of FIV and outcome. $T_{max} > 16$ seconds volume had the strongest association with FIV (beta coefficient = 0.596 p <0.001) and good outcome (odds ratio [OR] = 0.96 per 1 ml increase, 95% confidence interval [CI] = 0.95–0.97, $p < 0.001$). $T_{max} > 16$ seconds volume had the highest discriminative ability for good outcome (area under the curve [AUC] = 0.88,

95% CI = 0.842–0.909). A $T_{max} > 16$ seconds volume of ≤67 ml best identified subjects with favorable outcome (sensitivity = 0.91 and specificity = 0.73).

Interpretation: T_{max} target mismatch predicts radiological and clinical outcomes in patients with AIS with LVO receiving EVT within 24 hours from onset.

A growing body of data suggest that computed tomography perfusion (CTP) is a useful tool for the selection of patients with acute ischemic stroke (AIS) with anterior circulation large vessel occlusion (LVO) for endovascular treatment (EVT).[1] A favorable CTP profile was successfully used to establish the eligibility for EVT of patients with AIS with LVO in 2 late time window (6–24 hours) randomized controlled trials (RCTs), namely DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke)[2] and DAWN (Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention With Trevo),[3] and in 2 early time window (0–6 hours) RCTs, namely SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment)[4] and EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial).[5] In all these four CTP-guided RCTs,[2–5] patients with AIS were selected for therapy if meeting inclusion criteria consisting of a combination of parameters collectively called target mismatch. Although cut-off values of target mismatch varied across these studies, they were always automatically calculated with a dedicated software (RAPID; Rapid Processing of Perfusion and Diffusion; iSchemaView, Menlo Park, CA), based on the assumption that critically hypoperfused tissue is indicated by absolute time to the peak of the residual function (time to maximum concentration [T_{max}]) threshold values more than 6 seconds ($T_{max} > 6$ seconds) and ischemic core corresponds to relative cerebral blood flow (rCBF) threshold values less than 30% of normally perfused tissue (rCBF < 30%). In this model, the difference between $T_{max} > 6$ seconds and rCBF < 30% volumes (T_{max}-CBF mismatch) represents ischemic penumbra, whereas the ratio between $T_{max} > 6$ and rCBF < 30% volume is the mismatch ratio. Of note, CTP-based and non CTP-based RCTs shared the same limitation, a suboptimal patient selection as reflected by rates of functional dependency of around 50% despite successful recanalization.[2,3,6] Recent publications that use the GE CTP 4D show that a T_{max} value >16 seconds optimally identified follow-up infarct when non-contrast CT (NCCT) to recanalization time was within 90 minutes versus a T_{max} value >9.5 seconds that identified follow-up infarct best when early reperfusion was not achieved.[7] Thus, in patients who achieved recanalization >90 minutes after NCCT $T_{max} > 16$ seconds can be presumed to be the critically hypoperfused tissue. The difference between $T_{max} > 9.5$ seconds and $T_{max} > 16$ seconds volumes (T_{max}–T_{max} mismatch) can therefore be operationally considered as penumbra. T_{max} is a relatively robust parameter to measure on CTP. The aim of the present study was to assess the utility of this T_{max} based mismatch paradigm in predicting imaging and clinical outcomes. Additionally, this analysis sought to identify the optimal T_{max} volume thresholds that would identify patients with favorable functional outcome on follow-up.

Patients and Methods

This cohort study was approved by the local ethics boards of each participating site in which CT scans were performed and clinical information were recorded during routine clinical activity. Written informed consent was obtained from each patient or from their legally authorized representatives at admission or waived by the institutional review board.

Patient Selection

This was a retrospective analysis conducted on a prospectively collected cohort of consecutive patients with AIS with anterior circulation LVO treated with EVT and admitted from January 2013 to July 2017 at 2 academic Italian centers: S. Anna University Hospital of Ferrara and Careggi University Hospital of Florence. At both institutions, all patients presenting with suspected AIS with LVO, and no history of renal failure or contrast allergy routinely undergo NCCT, CT angiography (CTA) of the cervical and intracranial vessels and CTP at admission if they arrive at the hospital within 24 hours of symptom onset. If diagnosis of AIS is confirmed by neuroimaging findings, patients with AIS receive EVT according to the current recommended guidelines.[8,9] Patients were included if they presented to the emergency department with the following criteria: (1) NCCT Alberta Stroke Programme Early Computed Tomography Score (ASPECTS) ≥ 6; (2) diagnosis of AIS within 24 hours from witnessed symptom onset or time last seen well; (3) evidence of internal carotid artery (ICA) and/or middle cerebral artery (MCA) M1 or M2 segment occlusion on CTA; (4) CTP performed at admission; (5) selected for receiving EVT; and (6) follow-up NCCT imaging performed at 24 hours. Exclusion criteria were: (1) NCCT ASPECTS < 6; (2) age < 18 years; (3) pregnancy; (4) severe pre-stroke disability defined as modified Rankin Scale (mRS) ≥3; (5) detection of intracerebral hemorrhage on admission NCCT; (6) contraindications to iodinated contrast agent; (7) poor quality of CT acquisition

due to motion artifacts; and (8) inability to complete multi-modal CT protocol at baseline and/or 24-hour follow-up NCCT. NCCT ASPECTS (ASPECTS ≥ 6) was used for establishing patient eligibility for EVT before publication of the 2015 American Hospital Association / American Society of Anesthesiologists (AHA/ASA) guidelines,[9] based on the analysis by Puez and colleagues.[10] As suggested in the 2013 AHA/ASA guidelines,[8] CTP was used to provide additional information regarding diagnosis. No patient was excluded from the study due to a CTP unfavorable profile because CTP was not performed in patients with low ASPECTS (NCCT ASPECTS < 6). Figure S1 illustrates the cohort selection process.

Clinical Assessment

Demographic and clinical variables were collected by investigators blinded to the outcomes of interest. In particular, we obtained data on age, sex, pre-stroke functional status (mRS), known versus unknown stroke onset time, intravenous fibrinolysis with recombinant tissue plasminogen activator (r-TPA), time from onset to baseline CT, and time from baseline CT to EVT conclusion. Baseline stroke severity was measured with the National Institute of Health Stroke Scale (NIHSS). Clinical outcome was measured using mRS at 3 months. The mRS ≤ 2 and >2 were defined as good and poor outcome, respectively.

Imaging Acquisition

All imaging was conducted on 64-slice scanners (GE Healthcare, Waukesha, WI). NCCT helical scans were performed from the skull base to the vertex using the following imaging parameters: 120 kV, 340 mA, 4 × 5-mm collimation, 1 second/rotation, and table speed of 15 mm/rotation. CTA of the cervical and intracranial vessels was performed as follows: 0.7 ml/kg contrast (maximum 90 ml), 5- to 10-second delay from injection to scanning, 120 kV, 270 mA, 1 second/rotation, 1.25-mm thick slices, and table speed 3.75 mm/rotation. CTA covered from the carotid bifurcation to vertex. CTP studies were obtained with a dynamic first-pass bolus-tracking methodology according to a 2-phase imaging protocol, to avoid the truncation of time density curves, with axial shuttle mode. The 2-phase acquisition consisted of a first phase every 2.8 seconds for 60 seconds and an additional second phase every 15 seconds for 90 seconds, which started 5 seconds after the automatic injection of 40 ml of non-ionic contrast agent followed by a saline flush of 40 ml at the rate of 4 ml/s. Sections of 8 cm thickness were acquired at 5 mm slice thickness. The other acquisition parameters were 80 kV, 140 mAs, and 0.5 rotation time. All CTP source images were reconstructed with the standard filter and display field of view (DFOV) of 25 cm.

Imaging Processing and Analysis

The extent of early ischemic changes was evaluated on baseline NCCT using the ASPECTS methodology.[10] Each CTP study was processed by commercially available delay-insensitive deconvolution software (CT Perfusion 4D; GE Healthcare), as described elsewhere.[7] In-plane patient motion was corrected using an automated registration program included in the software, and the images with extreme motion at specific time points were manually removed, as needed, by visual inspection of the cine series and time density curve (TDC). For each study, the TDC for the arterial input function (AIF) and for venous output function (VOF) were measured from the basilar artery, ICA, or anterior cerebral artery and from the superior sagittal sinus, respectively using a 2 voxel × 2 voxel (in-slice) regions of interest (ROIs). The VOF-TDC was used to
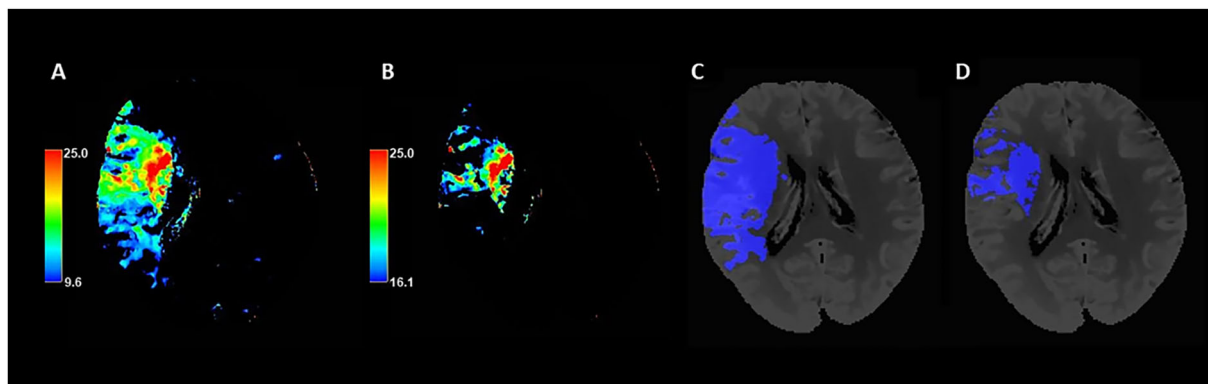
FIGURE 1: Automatic segmentation of critically hypoperfused tissue and infarct core volumes based on T_{max} >9.5seconds and >16 seconds threshold values. Panel A: Color coded CTP T_{max} map with scale set at 9.6 to 25 seconds. Panel B: Color coded CTP T_{max} map with scale set at 16.1 to 25 seconds. Panel C: T_{max} >9.5 seconds volume automatically segmented on CTP averaged images. Panel D: T_{max} >16 seconds volume automatically segmented on CTP averaged images. CTP = computed tomography perfusion; T_{max} = time to maximum concentration.

TABLE 1. Study Population Characteristics

	All	mRS 0–2	mRS 3–6	
	n = 393	n = 258	n = 135	p
Age, median (IQR), yr	73 (65–78)	72 (64–78)	75 (68–80)	<0.001
Sex, males, n (%)	215 (54.7)	136 (52.7)	79 (58.5)	0.272
Pre-stroke mRS				
0, n (%)	324 (82.4)	220 (85.3)	104 (77.0)	0.047
1, n (%)	56 (14.2)	33 (12.8)	23 (17.0)	
2, n (%)	13 (3.3)	5 (1.9)	8 (5.9)	
Admission NIHSS, median (IQR)	14 (10–20)	12 (9–15)	21 (17–23)	<0.001
ASPECTS score, median (IQR)	9 (8–10)	9 (8–10)	8 (7–10)	<0.001
Occlusion site				
Cervical ICA, n (%)	86 (21.9)	44 (17.1)	42 (31.1)	<0.001
Terminal ICA, n (%)	14 (3.6)	4 (1.6)	10 (7.4)	
MCA M1, n (%)	266 (67.7)	188 (72.9)	78 (57.8)	
MCA M2, n (%)	27 (6.9)	22 (8.5)	5 (3.7)	
r-TPA before EVT, n (%)	126 (32.1)	88 (34.1)	38 (28.1)	0.229
Time from onset to NCCT, median (IQR) minutes	279 (118–333)	281 (118–327)	257 (116–354)	0.961
Time from NCCT to reperfusion, median (IQR), minutes	124 (100–163)	112 (96–138)	151 (121–213)	<0.001
Collateral score				
0, n (%)	14 (3.6)	0 (0.0)	14 (10.4)	<0.001
1, n (%)	106 (27.0)	17 (6.6)	89 (65.9)	
2, n (%)	155 (39.4)	134 (51.9)	21 (15.6)	
3, n (%)	118 (30.0)	107 (41.5)	11 (8.1)	
mTICI score				
0, n (%)	34 (8.7)	8 (3.1)	26 (19.3)	<0.001
1, n (%)	24 (6.1)	1 (0.4)	21 (17.0)	
2a, n (%)	37 (9.4)	4 (1.6)	33 (24.4)	
2b, n (%)	63 (16.0)	40 (15.5)	23 (17.0)	
3, n (%)	235 (59.8)	205 (79.5)	30 (22.2)	
T$_{max}$ >9.5 seconds volume, median (IQR), ml	102 (55–160)	69 (41–112)	175 (121–218)	<0.001
T$_{max}$ >16 seconds volume, median (IQR), ml	30 (11–77)	20 (6–35)	93 (50–110)	<0.001
T$_{max}$ mismatch volume, median (IQR), ml	56 (35–91)	48 (29–73)	81 (51–117)	<0.001
T$_{max}$ mismatch ratio, median	2.7 (2.0–5.2)	3.7 (2.4–6.7)	2.0 (1.6–2.5)	<0.001
Final infarct volume, median (IQR), ml	29 (10–92)	16 (5–29)	103 (87–135)	<0.001
Hemorrhagic transformation ECASS II				
None, n (%)	252 (64.1)	195 (75.6)	57 (42.2)	<0.001
HT1, n (%)	63 (16.0)	41 (15.9)	22 (16.3)	
HT2, n (%)	32 (8.1)	11 (4.3)	21 (15.6)	
PH1, n (%)	20 (5.1)	7 (2.7)	13 (9.6)	
PH2, n (%)	26 (6.6)	4 (1.6)	22 (16.3)	
sICH, n (%)	39 (9.9)	7 (2.7)	32 (23.7)	<0.001
Any hemorrhagic transformation, n (%)	141 (35.8)	78 (57.8)	63 (24.4)	<0.001

ASPECTS = Alberta Stroke Program Early Computed Tomography Score; DSA = digital subtraction angiography; ECASS = European Cooperative Acute Stroke Study; EVT = endovascular treatment; HI1 = hemorrhagic infarction type 1; HI2 = hemorrhagic infarction type 2; ICA = internal carotid artery; IQR = interquartile range; MCA = middle cerebral artery; mRS = modified Rankin Scale; mTICI = modified treatment in cerebral infarction score; NCCT = non-contrast computed tomography; NIHSS = National Institute of Health Stroke Scale; PH1 = parenchymal hemorrhage type 1; PH2 = parenchymal hemorrhage type 2; r-TPA = recombinant tissue plasminogen activator; sICH = symptomatic intracerebral hemorrhage; T$_{max}$ = time to maximum concentration.

TABLE 2. Multivariable Predictors of Good Functional Outcome		
	OR (95% CI)	*p*
MODEL 1		
Age, yr	0.96 (0.92–1.01)	0.085
Admission NIHSS	0.84 (0.78–0.91)	<0.001
Collateral score	9.74 (4.90–19.34)	<0.001
mTICI score	5.03 (3.17–7.98)	<0.001
T_{max} >9.5 seconds volume, ml	0.98 (0.97–0.99)	<0.001
MODEL 2		
Admission NIHSS	0.83 (0.76–0.90)	<0.001
Collateral score	7.29 (3.76–14.13)	<0.001
mTICI score	4.76 (3.06–7.42)	<0.001
T_{max} >16 seconds volume, ml	0.96 (0.95–0.97)	<0.001
MODEL 3		
Admission NIHSS	0.82 (0.76.0.88)	<0.001
Collateral score	11.28 (5.91–21.54)	<0.001
mTICI score	4.53 (2.976.92)	<0.001
T_{max} mismatch volume, ml	0.98 (0.97–0.99)	<0.001
MODEL 4		
Admission NIHSS	0.80 (0.74–0.87)	<0.001
Collateral score	8.58 (4.69–15.72)	<0.001
mTICI score	4.18 (2.83–6.18)	<0.001
T_{max} mismatch ratio	1.17 (1.02–1.35)	0.026

Logistic regression with backward elimination at *p* < 0.1. Variables entered into the model: age, pre-stroke mRS, and NIHSS, ASPECTS, time from CT to recanalization, mTICI, collateral score, occlusion site; T_{max} parameters entered separately into different models. ASPECTS = Alberta Stroke Programme Early Computed Tomography Score; CI = confidence interval; CT = computed tomography; mRS = modified Rankin Scale; mTICI = modified treatment in cerebral infarction score; NIHSS = National Institute of Health Stroke Scale; OR = odds ratio; T_{max} = time to maximum concentration.

	AUC (95% CI)	
Tmax 9.5s	0.850 (0.810-0.884)	
Tmax 16s	0.878 (0.842-0.909)	
Tmax Mismatch Volume	0.715 (0.667-0.759)	
Tmax Mismatch Ratio	0.795 (0.752-0.834)	
	AUC difference (SE)	*p*
Tmax 16s vs Tmax 9.5s	0.028 (0.01)	0.026
Tmax 16s vs Tmax Mismatch Volume	0.163 (0.03)	<0.001
Tmax 16s vs Tmax Mismatch Ratio	0.082 (0.02)	<0.001

FIGURE 2: T_{max} volumes and T_{max} mismatch ratio optimal values for recognizing patients with AIS with good clinical outcome as calculated using ROC curves. AIS = acute ischemic stroke; AUC = area under the curve; CI = confidence interval; ROC = Receiver Operating Characteristic; SE = standard error; T_{max} = time to maximum concentration; T_{max} 9.5 seconds, T_{max} >9.5 seconds volume; T_{max} 16 seconds, T_{max} >16 seconds volume. AUC comparison was performed with DeLong test. Outcome of interest: modified Rankin Scale 0 to 2 at 90 days. [Color figure can be viewed at www.annalsofneurology.org]

correct for partial volume averaging in the AIF. CBF, cerebral blood volume (CBV), and T_{max} maps were generated for each patient by deconvolving the AIF from tissue TDCs. CBF, CBV, and T_{max} values were expressed in ml·min^{-1}·(100 g)$^{-1}$, ml·(100 g)$^{-1}$ and seconds, respectively. Average CTP maps were created by averaging the cine (dynamic) CTP source images over the duration of the first pass of contrast. These average CTP images were used to exclude cerebrospinal fluid (CSF) and skull from analysis using Hounsfield unit (HU) thresholds. Large blood vessels were automatically excluded from calculation by the software. Critically hypoperfused tissue and ischemic core volumes were defined as ischemic brain regions with T_{max} values >9.5 seconds and >16 seconds, respectively, and were automatically segmented and calculated by the software (Figure 1). According to the T_{max} target mismatch paradigm,[2,4,5] the difference between T_{max} > 9.5 seconds and T_{max} > 16 secondsvolumes (T_{max} mismatch) was considered as ischemic penumbra, and the ratio between T_{max} > 9.5 seconds and T_{max} > 16 seconds volumes was defined as the T_{max} mismatch ratio. Occlusion sites were identified on CTA and classified as cervical ICA, terminal ICA, middle cerebral artery (MCA) M1 segment, or MCA M2 segment occlusions. CTA collateral supply was graded on a 4-point scale according to a previously published scoring system in which collaterals were categorized as absent (score 0), >0% but ≤50% (score 1), >50% but <100% (score 2) and

TABLE 3. Test Characteristics of T$_{max}$ Volumes and T$_{max}$ Mismatch Ratio

	Sensitivity(95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
T$_{max}$ > 9.5 seconds volume ≤ 111.6 ml	0.76 (0.70–0.81)	0.82 (0.74–0.88)	0.89 (0.84–0.92)	0.64 (0.59–0.69)
T$_{max}$ > 16 seconds volume ≤ 67.0 ml	0.91 (0.87–0.94)	0.73 (0.64–0.80)	0.86 (0.83–0.89)	0.81 (0.74–0.87)
T$_{max}$ mismatch volume ≤ 58.3 ml	0.63 (0.57–0.69)	0.70 (0.61–0.77)	0.80 (0–75-0.84)	0.50 (0.45–0.55)
T$_{max}$ mismatch ratio > 2.5	0.70 (0.64–0.76)	0.79 (0.71–0.85)	0.86 (0.82–0.90)	0.58 (0.53–0.63)

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value; T$_{max}$ = time to maximum concentration. Outcome of interest: modified Rankin Scale 0 to 2 at 90 days.

100% (score 3) of the occluded territory.[11] Recanalization was assessed on conventional digital subtraction angiography (DSA) at the end of endovascular therapy using the modified treatment in cerebral ischemia (mTICI) scale.[12] Patients with mTICI score of 2b or 3 were considered as successfully recanalized, whereas patients with mTICI score ranging from 0 to 2a were classified as not. Hemorrhagic transformation (HT) was classified on NCCT at 24 hours from symptom onset/last known well according to the European Cooperative Acute Stroke Study (ECASS)-II criteria into four different categories: hemorrhagic infarction type 1 (HI1), HI type 2 (HI2), Parenchymal hemorrhage type 1 (PH1), and PH type 2 (PH2).[13] Symptomatic intracranial hemorrhage (sICH) was considered as any intracranial hemorrhage associated with a ≥4-point increase in NIHSS. Final infarct volume (FIV) was measured on follow-up NCCT at 24 hours after symptom onset/last known well with a multislice planimetric method by summation of the hypodense areas, manually traced on each slice in which they were detectable, multiplied by slice thickness.[14]

Statistical Analysis

Continuous variables were summarized as median (interquartile range [IQR]) or mean (standard deviation [SD]) as appropriate based on their distribution assessed with the Shapiro–Wilk test. Mann–Whitney test and Student's *t* test were used to compare continuous variables with non-normal and normal distributions, respectively. Categorical variables were summarized as count (percentage) and compared using the chi-square test. Good functional prognosis (defined as mRS 0–2) at 90 days from stroke onset and FIV and were the main outcomes of interest. Variables associated with good functional outcome were assessed using multivariable logistic regression, adjusting for age, admission NIHSS, ASPECTS score, collateral score, reperfusion status, and any variable showing significance at $p < 0.1$ in univariable analysis. Variables associated with FIV were explored with multivariable linear regression after testing for normality of residuals and

heteroskedasticity (with log-transformation of FIV). Models were adjusted for age, admission NIHSS score, ASPECTS score, collateral score, reperfusion status (defined as mTICI score 2b/3) and variables with $p < 0.1$ in univariable analysis. Backward elimination was used in both models to reach to a final parsimonious model that avoids model overfitting. Interaction terms were used in regression models to test the interaction among T$_{max}$ parameters, reperfusion status, and time to reperfusion (defined as time from baseline NCCT to DSA end). The utility of different T$_{max}$ volumes and T$_{max}$ mismatch ratio for identification of patients with good functional outcome was analyzed using area under the curve (AUC) Receiver Operating Characteristic (ROC) curves and optimal sensitivity, specificity, positive predictive value, and negative predictive values identified using the Youden Index. Comparison of models with T$_{max}$ > 9.5 seconds, T$_{max}$ > 16 seconds, mismatch volume and mismatch ratios as independent variables and the mRS 0 to 2 at 90 days as dependent variable was performed using the DeLong test.[15] A secondary analysis was focused on subjects presenting after 6 hours from symptom onset or time last seen well, with the same outcomes of interest explored in the main analysis. In this subgroup of patients, the model building strategy was the same as in the main analyses. Finally, a sensitivity analysis explored the diagnostic performance of T$_{max}$ parameters in patients who achieved mTICI (2b/3) post EVT versus those achieving mTICI ≤ 2a. All analyses were performed with the statistical packages SPSS version 21.0 (www.spss.com) and MedCalc (www.medcalc.org). Statistical significance was set at two-sided $p < 0.05$.

Results

We screened 477 potentially eligible patients with AIS with anterior circulation LVO, of whom 84 patients were excluded due to the presence of low ASPECTS (<6) on baseline NCCT, baseline intracerebral hemorrhage (n = 19), inability to complete multimodal CT protocol

TABLE 4. Univariable Predictors of Final Infarct Volume		
	B (SE)	*p*
Age, yr	0.151 (0.003)	0.003
Sex, male	−0.021 (0.066)	0.675
Admission NIHSS	0.581 (0.004)	<0.001
ASPECTS score	−0.239 (0.021)	<0.001
Carotid occlusion	0.209 (0.073)	<0.001
Unknown onset	−0.082 (0.092)	0.106
r-TPA before EVT	0.022 (0.071)	0.664
Time from onset to NCCT, minutes	0.035 (0.000)	0.492
Time from NCCT to DSA end, minutes	0.331 (0.000)	<0.001
Collateral score	−0.482 (0.034)	<0.001
mTICI 2b/3	−0.428 (0.069)	<0.001
T_{max} > 9.5 volume, ml	0.747 (0.000)	<0.001
T_{max} > 16 volume, ml	0.773 (0.000)	<0.001
T_{max} mismatch volume, ml	0.523 (0.001)	<0.001
T_{max} mismatch ratio	−0.460 (0.002)	<0.001

ASPECTS = Alberta Stroke Program Early Computed Tomography Score; B = beta coefficient; DSA = digital subtraction angiography; EVT = endovascular treatment; mTICI = modified treatment in cerebral infarction score; NCCT = non-contrast computed tomography; NIHSS = National Institute of Health Stroke Scale; r-TPA = recombinant tissue plasminogen activator; SE = standard error.
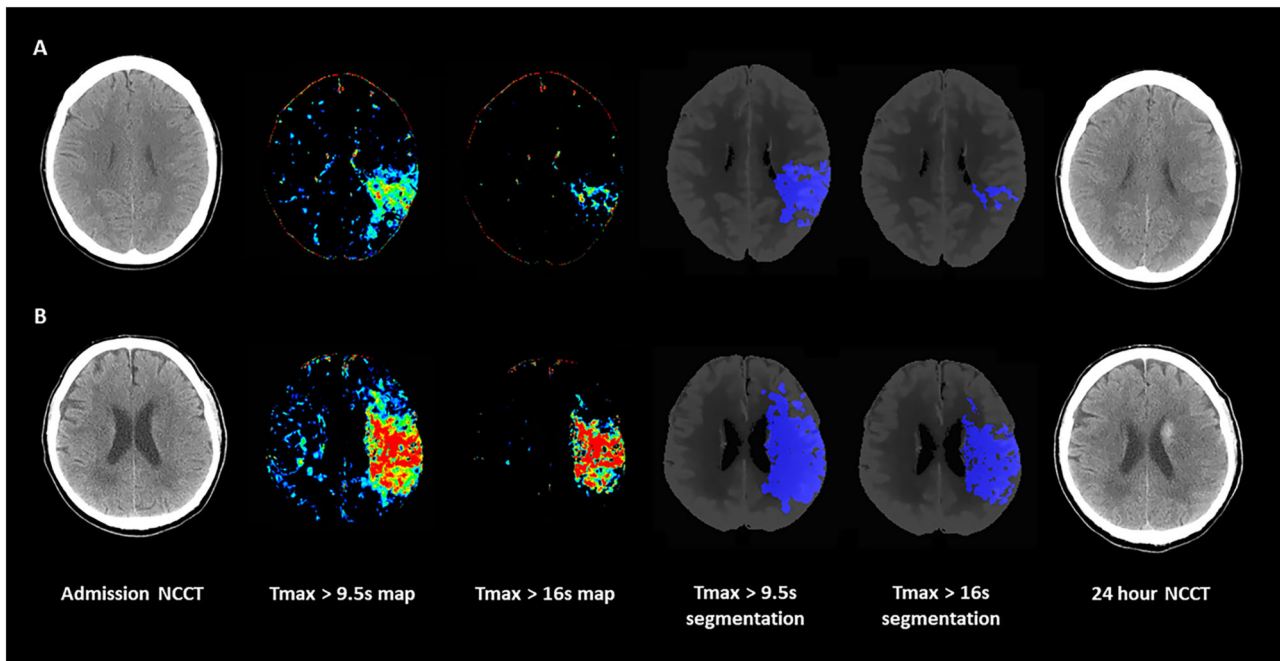
TABLE 5. Multivariable Predictors of Final Infarct Volume		
	B (SE)	*p*
MODEL 1		
Admission NIHSS	0.189 (0.004)	<0.001
Time from NCCT to DSA end, minutes	0.077 (0.000)	0.017
Collateral score	−0.090 (0.027)	0.012
mTICI 2b/3	−0.169 (0.049)	<0.001
T_{max} > 9.5 seconds volume, ml	0.544 (0.000)	<0.001
MODEL 2		
Admission NIHSS	0.203 (0.081)	<0.001
Time from NCCT to DSA end, minutes	0.075 (0.000)	0.017
Collateral score	−0.146 (0.048)	<0.001
mTICI 2b/3	0.596 (0.001)	<0.001
T_{max} > 16 seconds volume, ml	0.596 (0.001)	<0.001
MODEL 3		
Admission NIHSS	0.282 (0.004)	<0.001
Time from NCCT to DSA end, minutes	0.099 (0.000)	0.007
Collateral score	−0.199 (0.030)	<0.001
mTICI 2b/3	−0.203 (0.056)	<0.001
T_{max} mismatch volume, ml	0.333 (0.001)	<0.001
MODEL 4		
Admission NIHSS	0.320 (0.004)	<0.001
Time from NCCT to DSA end, minutes	0.110 (0.000)	0.003
Collateral score	−0.195 (0.031)	<0.001
mTICI 2b/3	−0.205 (0.057)	<0.001
T_{max} mismatch ratio	−0.307 (0.002)	<0.001

Logistic regression with backward elimination at *p* < 0.1. Variables entered into the model: age, NIHSS, ASPECTS, carotid occlusion, time from CT to recanalization, collateral score, mTICI 2b/3, T_{max}, T_{max} parameters entered separately into different models.
B = beta coefficient; CT = computed tomography; DSA = digital subtraction angiography; EVT = endovascular treatment; mTICI = modified treatment in cerebral infarction score; NCCT = non-contrast computed tomography; NIHSS = National Institute of Health Stroke Scale; r-TPA = recombinant tissue plasminogen activator; T_{max} = time to maximum concentration; SE = standard error.

at baseline and/or 24-hour follow-up NCCT (n = 15), poor quality of CT acquisition due to motion artifacts (n = 12), contraindications to iodinated contrast agent (known contrast allergy, renal failure) (n = 8), pre-stroke mRS >3 (n = 5), pregnancy (n = 3), and < 18 of age (n = 2). The study selection flowchart is illustrated in Figure S1.

Overall, 393 patients (median age = 73, IQR = 65–78, 54.7% men, median NIHSS = 14, IQR = 10–20) met study eligibility criteria. Of these, 314 were selected for EVT in the early (<6 hours) and 79 in the late (6–24 hours) time windows. Most of the included patients had a middle cerebral artery occlusion in the M1 segment and around one third of the study population received r-TPA before EVT. Table 1 summarizes the patient characteristics and shows the comparison

FIGURE 3: T$_{max}$ volumes in 2 patients with AIS and anterior circulation large vessel occlusion. Panel A: NCCT at admission, color coded CTP T$_{max}$ map with scale set at 9.6 to 25 seconds, Color coded CTP T$_{max}$ map with scale set at 16.1 to 25 seconds, T$_{max}$ > 9.5 seconds volume automatically segmented on CTP averaged images, T$_{max}$ > 16 seconds volume automatically segmented on CTP averaged images and NCCT at 24 hours in a 48 year-old patient with AIS and ischemic lesion in left MCA territory who presented the following T$_{max}$ parameters: critically hypoperfused tissue = 39.5 ml; core volume = 8.7 ml; penumbra volume = 30.8 ml; and mismatch ratio = 4.5. FIV was 7.2 ml and mRS at 3 months was 0. Panel B: NCCT at admission, color coded CTP T$_{max}$ map with scale set at 9.6 to 25 seconds, Color coded CTP T$_{max}$ map with scale set at 16.1 to 25 seconds, T$_{max}$ >9.5 seconds volume automatically segmented on CTP averaged images, T$_{max}$ >16 seconds volume automatically segmented on CTP averaged images and NCCT at 24 hours with hemorrhagic transformation in a 67 year old patient with AIS and ischemic lesion in left MCA territory who presented the following T$_{max}$ parameters: critically hypoperfused tissue = 158.0 ml; core volume = 87.4 ml; penumbra volume = 70.6 ml; mismatch ratio = 1.8. FIV was 131.2 ml and mRS at 3 months was 4. AIS = acute ischemic stroke; CTP = computed tomography perfusion; FIV = final infarct volume; MCA = middle cerebral artery; mRS = modified Rankin Scale; NCCT = non-contrast computed tomography; T$_{max}$ = time to maximum concentration.

between patients with good and poor functional outcome at 3 months. In univariable analyses, patients with good prognosis had lower T$_{max}$ > 9.5 seconds volumes, T$_{max}$ > 16 seconds volumes, T$_{max}$ mismatch volumes, and higher T$_{max}$ mismatch ratio. As shown in Table 2, all these associations between T$_{max}$ parameters and clinical outcome remained significant in multivariable logistic regression analysis after adjustment for potential confounders. No statistically significant interaction was noted among T$_{max}$ > 9.5 seconds volume, T$_{max}$ > 16 seconds volume, and reperfusion time or reperfusion status in association with 90 day clinical outcome (all *p* values for interaction > 0.1). Conversely, the association between T$_{max}$ mismatch volume and outcome was significant only in patients with time from CT to reperfusion <165 minutes (*p* value for interaction < 0.001). Moreover, T$_{max}$ mismatch ratio predicted functional outcome only in patients achieving a mTICI score of 2b/3 (*p* for interaction = 0.017). The ROC curve analysis shown in Figure 2 demonstrated that T$_{max}$ > 16 seconds volume had the highest discriminative ability (AUC 0.878; 95% confidence interval [CI] = 0.842–0.909) for 90 day clinical outcome.

When T$_{max}$ volumes and T$_{max}$ mismatch ratio were analyzed as dichotomous variables, the optimal cutoff points for predicting favorable 90-day clinical outcome were ≤111.6 ml for T$_{max}$ > 9.5 seconds, ≤67.0 ml for T$_{max}$ > 16 seconds, ≤58.3 ml for T$_{max}$ mismatch volume, and >2.5 for T$_{max}$ mismatch ratio. T$_{max}$ > 16 seconds volume ≤67.0 ml had the highest sensitivity (0.91; 95% CI = 0.87–0.94) for identification of subjects with favorable 90-day clinical outcome, whereas T$_{max}$ > 9.5 seconds volume ≤111.6 ml showed the highest specificity (0.82; 95% CI = 0.74–0.88). The test characteristics of different T$_{max}$ volumes are summarized in Table 3. In a secondary analysis stratified by mTICI status, results remained consistent. In particular, T$_{max}$ > 16 secondsvolume ≤67.0 ml remained the most sensitive (>0.90) parameter for the identification of patients with good prognosis, regardless of the degree of recanalization (Table S1).

As illustrated in Table 4, T$_{max}$ > 9.5 seconds volume, T$_{max}$ > 16 seconds volume, T$_{max}$ mismatch volume and T$_{max}$ mismatch ratio were all associated with the extent of FIV in unadjusted analysis. All T$_{max}$ variables remained independently associated with FIV (*p* < 0.001)

in multivariable linear regression (Table 5). When the analysis was restricted to 79 patients presenting 6 hours from stroke onset, of whom 47 (59.5%) had favorable functional outcome, the discriminative ability of T_{max} volumes and T_{max} mismatch volume remained good ($T_{max} > 9.5$ seconds volume, AUC 0.86, $p < 0.001$; $T_{max} > 16$ seconds volume AUC 0.88, $p < 0.001$; T_{max} mismatch volume AUC 0.74, $p < 0.001$; T_{max} mismatch ratio AUC 0.77, $p < 0.001$). In this subgroup of patients, the optimal value for predicting good outcome was similar to that obtained in overall analyses with $T_{max} > 9.5$ seconds volume (≤ 114.4 ml, sensitivity 0.72, specificity 0.84), $T_{max} > 16$ seconds volume (≤ 67.4 ml, sensitivity 0.89, and specificity 0.75) and T_{max} mismatch ratio (>2.8, sensitivity 0.62 and specificity 0.84), whereas T_{max} mismatch volume was lower than overall analysis (≤ 47.1 ml, sensitivity 0.53, and specificity 0.84). $T_{max} > 9.5$ seconds volume ≤ 114.4, ml and $T_{max} > 16$ seconds volume ≤ 67.4 ml were the most reliable parameters for identification of patients with favorable clinical outcome, with highest sensitivity (89%) and specificity (84%), respectively. Logistic and linear regression models showed that all T_{max} parameters remained independently associated with functional outcome and FIV in these late presenters, except for the lack of association between T_{max} mismatch ratio and outcome at 90 days (odds ratio [OR] = 1.11; 95% CI = 0.86–1.43; $p = 0.431$). Two illustrative cases showing the application of T_{max} volumes based on the established thresholds of >9.5 seconds and >16 seconds are depicted in Figure 3.

Discussion

The main finding of this study is that multiple CTP Tmax parameters are independently associated with functional outcome and with final infarct extent in patients with AIS undergoing EVT for LVO. In the context of RCTs showing the effectiveness of EVT in patients with AIS with LVO, CTP provided additional value in the early time window[1,4] and was mandatory in the late time window[2,3] for patients' selection. Inclusion criteria in these RCTs were based on the assumption that $T_{max} > 6$ seconds and rCBF < 30% threshold values represented critically hypoperfused tissue and ischemic core, respectively, and could be used to select patients for EVT. However, the identification of patients likely to benefit from EVT remains suboptimal as 50% of patients with AIS receiving successful reperfusion do not achieve a good functional outcome.[2,3,6] A recent study suggested that critically hypoperfused tissue and ischemic core could be better defined by $T_{max} > 9.5$ seconds and $T_{max} > 16$ seconds threshold values (GE CTP4D), respectively.[7] Our findings expand this previous observation demonstrating the ability of these parameters to predict radiological and clinical outcomes.

Our results are in line with previous investigations showing that in patients with AIS who underwent EVT < 6 hours[16] and 6–16 hours[17] after symptom onset/last known well time, ischemic core and hypoperfusion volumes were associated with FIV. In addition, as in a prior work on patients receiving EVT < 6 hours from onset,[18] we also confirm that the 2 variables indicating penumbra size, namely, T_{max} mismatch volumes and T_{max} mismatch ratio, predict FIV. The inclusion in our analysis of both patients who achieved reperfusion, in whom penumbral tissue is presumed to be saved, and patients who did not achieve reperfusion, in whom penumbra evolves into infarct, could in part explain our results. More interesting was the demonstration that $T_{max} > 9.5$ seconds volumes, $T_{max} > 16$ seconds volumes, T_{max} mismatch volumes, and T_{max} mismatch ratio were associated 90-day good outcome. This association was in line with data from RCTs[1–4] and other studies[18–20] suggesting that patients with AIS with favorable target mismatch profile achieved a good response to EVT. In this setting, the high predictive value of $T_{max} > 9.5$ seconds and the poor performance of T_{max} mismatch ratio for favorable outcome are not unexpected. Whereas $T_{max} > 9.5$ seconds volume represents critically hypoperfused tissue, including both ischemic core and ischemic penumbra, which strongly correlates with good prognosis, prior evidence suggests that mismatch ratios cannot be considered as robust markers of favorable outcome.[21] It is important to highlight that T_{max} volumes and mismatch ratio were associated with FIV and 90 day clinical outcomes independently from NIHSS, recanalization, and collateral score, which are considered strong predictors of radiological and clinical outcomes. In particular, T_{max} parameters and collaterals predicted outcome independently from each other, suggesting that T_{max} is not an epiphenomenon of collateral extent, but a complementary marker of delay in vessel filling of ischemic tissue.[22]

The optimal cutoffs for T_{max} parameters that predict good clinical outcome are similar to those in previous studies: a hypoperfusion volume ≤ 111.6 ml was comparable to the optimal value selected in DEFUSE 2 (<100 ml),[23] whereas an infarct volume ≤ 67.0 ml was similar to a cutoff point used in EXTEND-IA[5] and DEFUSE 3[2] (<70 ml). A penumbra volume ≤ 58.3 ml was very different from the cut-off values used in EXTEND-IA[5] (>10 ml), and in DEFUSE 3[2] and SWIFT PRIME[4] (>15 ml), but in agreement with the concept that a RAPID $T_{max} > 8$ seconds volume > 85 mL[24] indicates a malignant profile reflecting severely hypoperfused tissue destined to progress into infarction. A T_{max}

mismatch ratio >2.5 in this analysis was higher than the thresholds used in SWIFT PRIME (>1.2),[4] and in EXTEND-IA[5] and DEFUSE 3[2] (>1.8), but equivalent to the value proposed by other investigators (>2.6)[21] who recommended a larger mismatch ratio for better detecting the benefit of reperfusion therapies. Optimal thresholds to discriminate good outcome did not substantially change when the subset of patients presenting in the late time window were examined. Taken together, these data suggest that the possibility of achieving a favorable outcome increases in the presence of a small ischemic core volume, a significant mismatch between the extent of core and hypoperfusion, and a large, but not oversized, ischemic penumbra volume. Moreover, this study proposes a new CTP target mismatch based on specific threshold values of T$_{max}$ alone for identifying critically hypoperfused tissue (T$_{max}$ > 9.5 seconds) and ischemic core (T$_{max}$ > 16 seconds).

This study is not without limitations. First, as this study was based on retrospective analysis, our findings require prospective validation. Second, this was a non-randomized study consisting of a selected population in which eligibility for EVT was decided by local stroke team and data from patients not receiving EVT were lacking. Therefore, we cannot exclude the influence of unmeasured confounders and of selection bias in our analysis. Third, early presenters were more represented than late presenters, making the 2 groups unbalanced. Fourth, these results are conditional on the use of the GE CTP 4D algorithm; corresponding values for T$_{max}$ may need to be derived for other CTP algorithms.[25,26] Fifth, a comparison with RAPID thresholds as part of the DEFUSE 3 selection criteria was not performed, and therefore we are unable to comment whether T$_{max}$ target mismatch is different to DEFUSE 3 parameters based on T$_{max}$-CBF mismatch for differentiating good and poor radiological and clinical outcomes. Sixth, although consistent with some previous trials and meta-analyses,[2,27] the use of a dichotomized mRS may have reduced statistical power and neglected possible outcome shifts in the mRS range 3 to 6.[28] Seventh, the different devices used in our study period and the evolution of EVT technologies therefore during this period[29] may have influenced the results of this analysis. Finally, the exclusion of patients with low ASPECTS scores did not allow us to verify the rates of patients with unfavorable NCCT and favorable CTP profiles who achieved a good functional outcome that was reported to be about 60% in a recent study.[19]

In conclusion, we demonstrate the potential of a simple T$_{max}$ only target mismatch paradigm in predicting radiological and clinical outcomes in patients with AIS undergoing EVT both in the early and late time windows. Further prospective studies are warranted to clarify the actual applicability of T$_{max}$ target mismatch in selecting patients with AIS with LVO who can benefit from EVT.

Author Contributions

Conception and design of study: A.M. and E.F. Acquisition and analysis of data: all authors. Drafting manuscript and figures: all authors.

Potential Conflict of Interest

T.-Y.L. has a licensing agreement with GE Healthcare for the CT Perfusion software. Dr. Goyal participated to ESCAPE, REVASCAT, and SWIFT PRIME trials. Dr. Demchuk contributed to ESCAPE and REVASCAT trials and Dr. Menon was involved in the ESCAPE trial.

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