Stroke

BRIEF REPORT

# Penumbra Consumption Rates Based on Time-to-Maximum Delay and Reperfusion Status

## A Post Hoc Analysis of the DEFUSE 3 Trial

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**BACKGROUND AND PURPOSE:** In patients with acute large vessel occlusion, the natural history of penumbral tissue based on perfusion time-to-maximum ($T_{max}$) delay is not well established in relation to late-window endovascular thrombectomy. In this study, we sought to evaluate penumbra consumption rates for $T_{max}$ delays in patients with large vessel occlusion evaluated between 6 and 16 hours from last known normal.

**METHODS:** This is a post hoc analysis of the DEFUSE 3 trial (The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke), which included patients with an acute ischemic stroke due to anterior circulation occlusion within 6 to 16 hours of last known normal. The primary outcome is percentage penumbra consumption, defined as (24-hour magnetic resonance imaging infarct volume–baseline core infarct volume)/($T_{max}$ 6 or 10 s volume–baseline core volume). We stratified the cohort into 4 categories based on treatment modality and Thrombolysis in Cerebral Infarction (TICI score; untreated, TICI 0-2a, TICI 2b, and TICI3) and calculated penumbral consumption rates in each category.

**RESULTS:** We included 141 patients, among whom 68 were untreated. In the untreated versus TICI 3 patients, a median (interquartile range) of 53.7% (21.2%–87.7%) versus 5.3% (1.1%–14.6%) of penumbral tissue was consumed based on $T_{max}$ >6 s ($P$<0.001). In the same comparison for $T_{max}$>10 s, we saw a difference of 165.4% (interquartile range, 56.1%–479.8%) versus 25.7% (interquartile range, 3.2%–72.1%; $P$<0.001). Significant differences were not demonstrated between untreated and TICI 0-2a patients for penumbral consumption based on $T_{max}$ >6 s ($P$=0.52) or $T_{max}$ >10 s ($P$=0.92).

**CONCLUSIONS:** Among extended window endovascular thrombectomy patients, $T_{max}$ >10-s mismatch volume may comprise large volumes of salvageable tissue, whereas nearly half the $T_{max}$ >6-s mismatch volume may remain viable in untreated patients at 24 hours.

**Key Words:** cerebral infarction ■ ischemic stroke ■ perfusion ■ reperfusion ■ thrombectomy



Endovascular thrombectomy (EVT) is the standard of care in eligible patients with acute ischemic stroke and proximal large artery occlusion presenting within 24 hours from last known normal time.[1] Patient selection has varied across studies and remains a subject of controversy. Perfusion-based imaging has been utilized to select patients for EVT and studies have shown that utilizing time-to-maximum ($T_{max}$) delay thresholds can help select patients with penumbral tissue who would benefit from EVT in the extended treatment window.[2,3]

Prior studies have shown that noninfarcted tissue with $T_{max}$>5.6-s delay may best identify penumbral tissue,[4] that noninfarcted tissue with $T_{max}$>10-s delay is likely destined to progress to infarction despite successful reperfusion,[5]

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## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **DEFUSE-3** | The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke |
| **EVT** | endovascular thrombectomy |
| **MR** | magnetic resonance |
| **TICI** | Thrombolysis in Cerebral Infarction |
| **Tmax** | time-to-maximum |

and that optimal thresholds may be modified by time from perfusion imaging to reperfusion.[6] These studies were limited by their small sample sizes, use of older generation devices in EVT treated patients, and the paucity of data on extended window patients for whom perfusion imaging–based selection is most beneficial.[1]

In this study, we aimed to determine the degree of penumbra consumption for the $T_{max}$ delay thresholds of 6 and 10 s in patients arriving in the extended (6–16 hour) window based on treatment modality and degree of reperfusion.

# METHODS

## Patient Cohort

We used STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) for reporting and the checklist is included in the Data Supplement. Institutional review board approval was waived. This is a post hoc analysis of DEFUSE 3[2] trial (The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) using publicly available data obtained from the National Institute of Neurological Disorders and Stroke at https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets. DEFUSE 3 randomized patients with acute ischemic stroke and proximal anterior circulation large vessel occlusion and the presence of a target mismatch profile on computed tomography or magnetic resonance (MR) perfusion to EVT plus best medical treatment versus best medical treatment only. In this study, we included DEFUSE 3 patients who had perfusion imaging data at baseline and an MR imaging at 24 hours with final infarct volume measurement. We excluded patients with no baseline $T_{max}$>10-s delay because it did not permit analysis of the primary outcome.

## Predictors and Primary Outcome

The primary outcome was percentage penumbra consumption defined as (24-hour infarct volume–baseline core infarct volume)/($T_{max}$ >6 or >10 s volume–baseline core infarct volume).[7] The neuroimaging measurement of $T_{max}$ delay–based mismatch volumes was performed at baseline with a mix of computed tomography perfusion and MR imaging, both processed using RAPID software (IschemaView: Menlo Park, CA). The RAPID software measured core volume on the apparent diffusion coefficient MR imaging with a defined threshold level of <620 and on computed tomography perfusion as a relative cerebral blood flow <30% of the contralateral hemisphere. Infarct volume at 24 hours was restricted to measurements made with MR imaging. Details regarding imaging adjudications were previously published.[2]

## Variables of Interest

The variables of interest in our study were: time from last known normal to reperfusion and the degree of reperfusion in patients randomized to endovascular treatment assessed by two independent raters and categorized in Thrombolysis in Cerebral Infarction (TICI) 0-2a, TICI 2B, and TICI 3.[2]

## Statistical Analysis

We reported the median percent penumbral consumption between 4 categories (untreated, TICI 0-2a, TICI 2b, and TICI3) and tested for differences with the Kruskal Wallis test and between 2 categories with the Wilcoxon rank-sum test. We report the correlation coefficient between time to reperfusion and Tmax>10-s penumbral consumption in treated patients and the results of a linear regression model fit to $T_{max}$>10-s penumbral consumption with the interaction term of time to reperfusion×TICI. As a sensitivity analysis, we used log-transformed values of our outcomes to reduce right skew and determine if the results were consistent with the primary analysis. Stata 16.1 (StataCorp, College Station, TX) was used for all analyses, and significance was defined as a $P$ value <0.05.

# RESULTS

Among patients enrolled in DEFUSE 3, 141 patients met the inclusion criteria (Study Flow Chart; Figure) with a mean age was 68.3±13.6 years and 49.7% were women (Table I in the Data Supplement). Among the 141 patients, 68 were untreated, 14 had TICI 0-2a, 44 had TICI 2b, and 15 had TICI 3. The difference in percentage penumbral consumption between the groups was highly significant for $T_{max}$>6 s ($P$<0.001), $T_{max}$>10-s ($P$=0.004), and the log transformation of both ($P$<0.001), which reduced inherent skew. Furthermore, time from stroke onset or last known normal to reperfusion was not associated with penumbral consumption ($r$=0.002, $P$=0.971), and the interaction term with TICI score also lacked significance ($P$=0.561).

## Medical Arm

In untreated patients, a median (interquartile range) of 53.8% (21.2%–87.7%) of penumbral tissue was consumed based on $T_{max}$>6 s as opposed to 165.4% (56.1%–479.8%) of penumbral tissue based on $T_{max}$>10 s (Table; Figure I in the Data Supplement).

## Endovascular Arm

In patients achieving TICI 3 reperfusion, a median (interquartile range) of 5.3% (1.1%–14.6%) of penumbral tissue was consumed based on $T_{max}$>6 s and 25.7% (3.2%–72.1%) of penumbral tissue based on $T_{max}$>10 s (Table; Figure I in the Data Supplement). In treated patients with TICI 2b reperfusion, the rates were

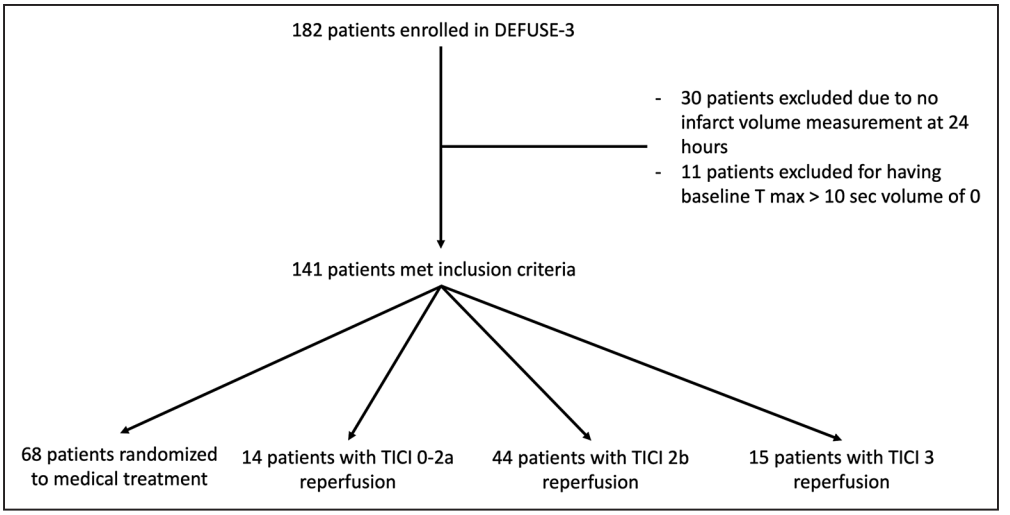


**Figure. Patient flow chart.**
DEFUSE-3 indicates The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; TICI, Thrombolysis in Cerebral Infarction; and $T_{max}$, time-to-maximum.

30.1% (18.9%–89.3%) based on $T_{max}$ >6 s and 117.5% (34.2%–297%) based on $T_{max}$ >10 s (Table; Figure I in the Data Supplement). Finally, in treated patients with TICI 0-2a reperfusion, penumbral consumption rates were 32.1% (23.3%–113.6%) based on $T_{max}$>6 s and 185.3% (88.8%–347.7%) based on $T_{max}$>10 s.

## DISCUSSION

Contrary to prior studies which identified $T_{max}$>10 s as malignant tissue destined to infarction,[8] we show that in patients selected for EVT in the extended window, at least 75% of penumbral tissue with $T_{max}$>10-s delay can be salvaged with complete reperfusion via new-generation devices. TICI 3 reperfusion, compared with untreated patients, created a 10-fold reduction in penumbral consumption for $T_{max}$>6-s delay and 6-fold reduction in penumbral consumption for $T_{max}$>10-s delay. The percentage of penumbral consumption in our study was higher in patients with no or partial reperfusion after EVT. This highlights the benefit of complete reperfusion in limiting penumbral consumption even in viable tissue but with $T_{max}$>10-s delay. In addition, decreased time from perfusion imaging acquisition to reperfusion has been shown to limit penumbral consumption[5,6,8] and thus achieving timely reperfusion is critical in salvaging critically hypoperfused brain tissue.

However, in medically treated patients, only 50% of penumbral tissue with $T_{max}$>6-s delay was consumed at 24 hours. This finding may be related to our assessing penumbral consumption using 24-hour imaging and while consumption of penumbral tissue based on $T_{max}$>6-s delay continues beyond 24 hours. If true, this may suggest an opportunity to investigate the benefit of reperfusion therapy for select patients even beyond the 24-hour time window and for neuroprotective agents to be studied in this window for patients who are not reperfused successfully. Alternatively, it is possible that the $T_{max}$>6-s delay threshold in the extended window, or more generally among slow progressors, does not accurately define penumbral tissue.

Our study has several limitations including the small sample size, lack of brain imaging beyond 24 hours, our not using a voxel-to-voxel comparison for assessment of penumbral consumption across $T_{max}$ delay thresholds, the use of only 2 $T_{max}$ thresholds in our analysis, and limited generalizability, given the inclusion/exclusion criteria for the DEFUSE 3 trial which is a potential source of bias.

## CONCLUSIONS

In extended time window EVT, TICI 3 reperfusion achieved a 10-fold reduction in penumbral consumption for $T_{max}$>6 s volumes and 6-fold reduction for $T_{max}$>10-s

**Table. Percentage of Penumbral Consumption Based on Baseline $T_{max}$ Delay Thresholds**

| Penumbral consumption | $T_{max}$>6 s (median, IQR) | $T_{max}$>10 s (median, IQR) |
|---|---|---|
| Medical arm (n=68) | 53.8% (21.2%–87.7%) | 165.4% (51.0%–378.6%) |
| Endovascular arm with TICI 0–2a (n=14) | 32.1% (23.3%–113.6%) | 185.3% (88.8%–347.7%) |
| Endovascular arm with TICI 2b (n=44) | 30.1% (18.9%–89.3%) | 117.5% (34.2%–298.0%) |
| Endovascular arm with TICI 3 (n=15) | 5.3% (1.1%–14.6%) | 25.7% (3.2%–72.1%) |

IQR indicates interquartile range; TICI, Thrombolysis in Cerebral Infarction; and $T_{max}$, time-to-maximum.

volumes, as compared to untreated subjects. In untreated patients, future studies with delayed imaging outcomes are needed to determine the optimal $T_{max}$ threshold that defines penumbral tissue in patients with proximal anterior circulation large vessel occlusion.

## ARTICLE INFORMATION

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