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N.B. Rex, R.V. McDonough, J.M. Ospel, N. Kashani, A. Sehgal, J.C. Fladt, R.A. McTaggart, R. Nogueira, B. Menon, A.M. Demchuk, M. Tymianski, M.D. Hill and M. Goyal

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ABSTRACT

BACKGROUND AND PURPOSE: Although reperfusion is associated with improved outcomes in patients with acute ischemic stroke undergoing endovascular treatment, many patients still do poorly. We investigated whether CTP modifies the effect of near-complete reperfusion on clinical outcomes, ie, whether poor clinical outcomes despite near-complete reperfusion can be partly or fully explained by CTP findings.

MATERIALS AND METHODS: Data are from the Safety and Efficacy of Nerinetide in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1) trial. Admission CTP was processed using RAPID software, generating relative CBF and CBV volume maps at standard thresholds. CTP lesion volumes were compared in patients with-versus-without near-complete reperfusion. Associations between each CTP metric and clinical outcome (90-day mRS) were tested using multivariable logistic regression, adjusted for baseline imaging and clinical variables. Treatment-effect modification was assessed by introducing CTP lesion volume $\times$ reperfusion interaction terms in the models.

RESULTS: CTP lesion volumes and reperfusion status were available in 410/1105 patients. CTP lesion volumes were overall larger in patients without near-complete reperfusion, albeit not always statistically significant. Increased CBF $<34\%$, CBV $<34\%$, CBV $<38\%$, and CBV $<42\%$ lesion volumes were associated with worse clinical outcome (ordinal mRS) at 90 days. CTP core lesion volumes did not modify the treatment effect of near-complete recanalization on clinical outcome.

CONCLUSIONS: CTP did not modify the effect of near-complete reperfusion on clinical outcomes. Thus, CTP cannot explain why some patients with near-complete reperfusion have poor clinical outcomes.

ABBREVIATIONS: AIS = acute ischemic stroke; eTICI = expanded TICI; EVT = endovascular treatment; LVO = large-vessel occlusion; rCBF = relative CBF

The goal of endovascular treatment (EVT) of stroke is reperfusion of ischemic brain tissue via recanalization of the occluded blood vessel, the latter of which is measured by the expanded TICI (eTICI) score. While recanalization is almost

always required to achieve good clinical outcomes, it is by no means a guarantee for favorable outcome.¹ On the contrary, many patients in whom near-complete recanalization can be achieved (final eTICI 2c–3) still do poorly. The reasons for this apparent discrepancy are manifold and may include “futile” recanalization (leading to reperfusion of tissue that is already irreversibly damaged), postprocedural complications (eg, pulmonary embolism, aspiration, and urinary tract infections), as well as lacking reperfusion at the tissue level despite angiographic vessel recanalization as assessed by the eTICI score.

CTP is often performed as part of acute ischemic stroke (AIS) imaging in addition to noncontrast CT and CTA alone.^{2–4} It relies on tracking of a contrast bolus after IV injection of iodinated contrast via repeat imaging (45–90 times). These repeat measurements are then used to generate time-to-maximum, relative CBF (rCBF), and CBV maps. These various CTP measures are thought to capture the “depth” of ischemia and may explain the discrepancy between near-complete angiographic reperfusion and poor clinical outcomes in some patients undergoing EVT.

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From the Department of Diagnostic Imaging (N.B.R., R.A.M.), Brown University, Providence, Rhode Island; Departments of Diagnostic Imaging (N.B.R., R.V.M., J.M.O., B.M., A.M.D., M.D.H., M.G.), and Clinical Neurosciences (J.M.O., A.S., J.C.F., B.M., A.M.D., M.D.H., M.G.), University of Calgary, Calgary, Alberta, Canada; Department of Neurosurgery (N.K.), University of Saskatchewan, Saskatoon, Saskatchewan, Canada; Department of Neurology and Stroke Center (J.C.F.), University Hospital Basel, Basel, Switzerland; Department of Neurology and Neurosurgery (R.N.), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and NoNO Inc (M.T.), Toronto, Ontario, Canada.

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Please address correspondence to Mayank Goyal, MD, Departments of Diagnostic Imaging and Clinical Neurosciences, Foothills Medical Centre, 1403 29th St NW, University of Calgary, Calgary, Alberta, T2N2T9, Canada; e-mail: mgoyal@ucalgary.ca; @johanna_ospel; @rosevcmd; @mayank_G0; @joachimfladt

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We therefore, investigated whether CTP parameters modify the effect of reperfusion status on clinical outcomes in patients with AIS undergoing EVT and whether CTP information improves prognostic performance regarding clinical outcome in patients with EVT with near-complete reperfusion.

MATERIALS AND METHODS

Patient Sample

This study is a post hoc analysis of the Safety and Efficacy of Nerinetide in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1), trial ([clinicaltrials.gov: NCT02930018](https://clinicaltrials.gov/ct2/show/study/NCT02930018)), a double-blind, multicenter, randomized controlled trial that evaluated the efficacy of nerinetide in patients with AIS who underwent EVT.⁵ Patients were randomly allocated to receive either IV nerinetide versus a placebo in addition to best medical management, including IV alteplase if indicated. Inclusion criteria were as follows: the presence of a large-vessel occlusion (LVO), moderate-to-good collateral circulation, ASPECTS of ≥ 5 , at least 18 years of age, NIHSS score of >5 , functional independence before the stroke (Barthel index >90), and time since last known well of <12 hours. Perfusion imaging was performed as part of clinical routine at each respective site, but it was not mandated by the trial. Appropriate ethics and local regulatory approval were required at each site, as was signed informed consent from participants, a legally authorized representative, or the investigators using 2-physician consent when required by national laws or regulations.

Imaging Analysis. All imaging was assessed by a Central Imaging Core Lab that was blinded to treatment allocation and clinical outcomes.

The ASPECTS was assessed on baseline NCCT. Occlusion location on multiphase CTA was reported as either the terminal ICA or the M1 or M2 segment of the MCA.

Perfusion source images, when available, were processed using RAPID perfusion software, Version 5.2.2 (iSchemaView) to generate standard rCBF and CBV volumes. The standard RAPID workflow followed for each patient in this study generated 4 rCBF volumes ($<20\%$, $<30\%$, $<34\%$, $<38\%$), and 3 CBV volumes ($<34\%$, $<38\%$, $<42\%$). These thresholds were chosen because they are the values provided in the standard RAPID output that have been previously validated⁶ and are commonly used in clinical practice. All output DICOMs were converted to NIfTI using dcm2niix (<http://www.github.com/rordenlab/dcm2niix>) and then underwent automated segmentation using color-based thresholding in Python, Version 3.10 (<http://www.python.org>). Segmentation volumes for each threshold were extracted using 3D Slicer, Version 5.0.2 (<http://www.slicer.org>). Segmentation volumes were extracted using the built-in Segmentation Statistics functionality of 3D Slicer. All Slicer-generated output volumes were confirmed and rounded to the nearest milliliter of the original RAPID generated output, validating the fidelity of this approach. Key Python functions necessary for reproduction of feature extraction and processing are detailed on Github (https://github.com/naterex23/RAPID_Perfusion_Processing), and the additional Python source code is available on reasonable request.

eTICI was assessed on the final intracranial DSA run. Near-complete reperfusion was defined as eTICI 2c–3, ie, $>90\%$ reperfusion of the target territory.

Outcome Measures. The primary outcome was functional outcome as measured by the mRS at 90 days, which was assessed blinded to treatment allocation. To perform receiver operating characteristic analysis, we dichotomized the mRS into good outcome (mRS 0–2) versus no good outcome (mRS 3–6).

Statistical Analysis. Baseline characteristics, clinical outcomes, and CTP lesion volumes in patients with-versus-without near-complete recanalization were reported using descriptive statistics as appropriate.

We then performed adjusted ordinal logistic regression using the ordinal mRS at 90 days as a dependent variable and the following, prespecified independent variables: age (in years), sex, NIHSS score, treatment allocation (nerinetide versus placebo), alteplase treatment, baseline ASPECTS, collateral score (poor versus moderate versus good), time from onset to CT, final eTICI (eTICI 2c–3 versus none), and CTP lesion volume. Separate models were constructed for each CTP parameter (ie, CBF $<20\%$, CBF $<30\%$, $<34\%$, CBF $<38\%$, CBV $<34\%$, CBV $<38\%$, CBV $<42\%$). Each model included a multiplicative two-by-two CTP lesion volume $\times$ near-complete reperfusion interaction term to investigate whether CTP lesion volumes modify the effect of near-complete reperfusion on outcome.

To further investigate whether CTP lesion volumes could explain the variance in clinical outcomes in patients with near-complete reperfusion, we compared CTP lesion volumes in patients with eTICI 2c–3 with versus without good clinical outcomes. We further compared the prognostic performance of logistic regression models containing prespecified baseline variables (age, sex, NIHSS score, treatment allocation, alteplase treatment, baseline ASPECTS, collateral score [poor versus moderate versus good], time from onset to CT imaging) versus those containing additional CTP lesion volumes. Model performance was assessed using the area under the curve and the Akaike and Bayesian information criterion.

In case the initial interaction analyses were not significant, the above-mentioned subgroup analyses in patients with eTICI 2c–3 were considered purely exploratory.

Statistical analysis was conducted using STATA 17 (StatCorp), and *P* values $<.05$ were considered statistically significant.

RESULTS

Patient Characteristics

Of the 1105 patients enrolled in ESCAPE-NA1, 426 had available CTP imaging. CTP quality was judged to be insufficient for analysis in 13 patients, and final reperfusion status could not be assessed in 3 patients, leaving 410 patients for the analysis. Table 1 compares baseline and treatment characteristics of patients with versus without near-complete reperfusion, which did not differ significantly between the groups. Although CTP lesion volumes were nominally larger in patients without near-complete reperfusion irrespective of the CTP threshold used, this difference

Table 1: Baseline and treatment characteristics of patients with-versus-without near-complete reperfusion (eTICI 2c–3)

Variable	Near-Complete Reperfusion (n = 186)	No Near-Complete Reperfusion (n = 224)	P Value
Age (median) (IQR) (yr)	71.1 (61.2–80.1), n = 186	69.3 (58.4–79.6), n = 224	.12
Baseline NIHSS (median) (IQR)	18 (12–21), n = 186	17 (13–20), n = 224	.29
History of diabetes (No.) (%)	31/186 (16.7%)	46/224 (20.5%)	.55
History of past stroke/TIA (No.) (%)	24/186 (12.9%)	33/224 (14.7%)	.67
History of prior cardiac disease (No.) (%)	49/186 (26.3%)	47/224 (21.0%)	.24
Baseline ASPECTS (median) (IQR)	8 (7–9), n = 186	8 (6–8), n = 224	.13
Collateral score (No.) (%)			.06
Poor	2/186 (1.1%)	11/218 (5.1%)	
Moderate	154/186 (82.8%)	178/218 (81.7%)	
Good	30/186 (16.1%)	29/218 (13.3%)	
Study drug to reperfusion time (median) (IQR) (min)	22 (9–39), n = 182	26 (12–52), n = 170	.17
Terminal ICA occlusion (No.) (%)	28/186 (15.1%)	44/223 (19.7%)	.24
IV alteplase (No.) (%)	110/186 (59.1%)	122/224 (54.5%)	.37
IV nerinide (No.) (%)	89/186 (47.9%)	107/224 (47.8%)	1.00
Stent retriever as first-line device (No.) (%)	150/204 (73.5)	142/176 (80.7)	.103
Carotid stent placement during EVT	22/110 (20.0)	12/81 (14.8)	.445

Note:—IQR indicates interquartile range.

Table 2: CTP lesion volumes in patients with-versus-without near-complete reperfusion^a

CTP Parameter (Median) (IQR)	Near-Complete Reperfusion (n = 186)	No Near-Complete Reperfusion (n = 224)	P Value
CBF <20%	0 (0–0)	0 (0–7.5)	<.01
CBF <30%	7.6 (0–28.1)	12.0 (0–32.1)	.06
CBF <34%	14.3 (2.7–39.4)	19.1 (5.2–47.2)	.10
CBF <38%	21.3 (7.1–54.8)	26.4 (9.9–60.9)	.20
CBV <34%	5.1 (0–28.1)	9.8 (0–33.3)	.07
CBV <38%	6.7 (0–35.6)	13.3 (0–39.0)	.048
CBV <42%	10.1 (0–41.2)	17.9 (4.6–46.0)	.06

Note:—IQR indicates interquartile range.

^a Data in columns 2 and 3 are medians and interquartile ranges.

Table 3: CTP lesion volumes in patients with near-complete reperfusion who did and did not achieve good outcome at 90 days^a

CTP Parameter (Median) (IQR)	Near-Complete Reperfusion with No Good Outcome (n = 54)	No Near-Complete Reperfusion with Good Outcome (n = 132)	P Value
CBF <20%	0 (0–6.9)	0 (0–0)	.02
CBF <30%	12.2 (4.4–38.6)	6.0 (0–22.2)	.01
CBF <34%	20.6 (8.1–53.0)	13.0 (0–33.6)	.02
CBF <38%	33.4 (13.4–73.0)	18.4 (6.6–46.4)	.0495
CBV <34%	12.2 (2.9–43.2)	0 (0–20.6)	<.01
CBV <38%	19.0 (4.9–54.2)	4.7 (0–23.1)	<.01
CBV <42%	21.8 (6.4–66.7)	6.5 (0–28.5)	<.01

Note:—IQR indicates interquartile range.

^a When comparing the performance of multivariable logistic regression models in predicting good outcome at 90 days in patients with near-complete recanalization, model performance slightly increased and information loss decreased when CTP lesion volumes were added in addition to baseline variables, though the area under the curve confidence intervals overlapped (Table 4). Data in columns 2 and 3 are medians and interquartile ranges.

reached statistical significance only when using the CBF <20% threshold (Table 2).

Multivariable Logistic Regression with Two-by-Two Interaction Terms

In the adjusted analysis, none of the CTP lesion volume × reperfusion status interaction terms were significant; thus, the subgroup analyses below were considered exploratory. Of all the CTP lesion volumes, CBF <34% (adjusted OR = 1.01; 95% CI, 1.0001–1.017 per milliliter increase), CBV <34% (adjusted OR =

1.01; 95% CI, 1.001–1.02 per milliliter increase), CBV < 38% (adjusted OR = 1.01; 95% CI, 1.001–1.02 per milliliter increase), and CBV <42% (adjusted OR = 1.01; 95% CI, 1.000–1.02 per milliliter increase) were predictors of clinical outcome (ordinal mRS) at 90 days.

Exploratory Subgroup Analyses in Patients with Near-Complete Reperfusion

In patients with near-complete reperfusion (eTICI 2c–3), CTP lesion volumes were higher in patients without-versus-with good outcome (Table 3). Model performance as measured by the AUC, AIC, BIC and pseudo-R squared improved slightly when CTP parameters were included in the model, although the AUC 95% CI overlapped (Table 4).

DISCUSSION

This post hoc analysis of the ESCAPE-NA1 trial suggests that patients having undergone EVT with small CTP lesion volumes at baseline generally do better compared with those with larger CTP lesions, but CTP did not modify the effect of near-complete reperfusion on

clinical outcomes. In other words, CTP is a prognostic marker for post-EVT outcomes, but it cannot explain why some patients have poor outcomes despite near-complete recanalization.

There are many reasons why patients undergoing successful EVT with near-complete recanalization still do not do well. For example, reperfusion injury may lead to formation of reactive oxygen species, apoptosis may be induced by oxidative stress, and edema progression or poststroke complications such as pulmonary embolism or pneumonia may occur.^{7,8} Another potential explanation is futile reperfusion, ie, reperfusion of tissue that is already irreversibly damaged. Establishing reperfusion in such

Table 4: Performance of multivariable logistic regression models without and with CTP lesion volumes in predicting good outcome at 90 days in patients with near-complete recanalization

Model	Pseudo-R ²	BIC	AIC	AUC (95% CI)
Baseline variables only ^a	0.302	203.6	174.5	0.766 (0.718–0.813)
Baseline variables + CBF <20% volume	0.336	201.1	168.9	0.782 (0.735–0.829)
Baseline variables + CBF <30% volume	0.357	196.4	164.2	0.785 (0.739–0.831)
Baseline variables + CBF <34% volume	0.359	196.0	163.8	0.784 (0.738–0.830)
Baseline variables + CBF <38% volume	0.359	195.8	163.6	0.781 (0.735–0.828)
Baseline variables + CBV <34% volume	0.343	199.5	167.2	0.778 (0.731–0.824)
Baseline variables + CBV <38% volume	0.346	198.8	166.5	0.779 (0.732–0.825)
Baseline variables + CBV <42% volume	0.349	198.1	165.9	0.779 (0.732–0.825)

Note:—AIC indicates Akaike information criterion; BIC, Bayesian information criterion; AUC, area under the curve; Pseudo-R², pseudo-R squared.

^aBaseline variables were prespecified and included age (in years), sex, NIHSS, treatment allocation (nerinetide versus placebo), alteplase treatment, baseline ASPECTS, collateral score (poor versus moderate versus good), and time from onset to CT imaging.

tissue only exposes the patient to risk of hemorrhage, without restoring brain function. The single most important parameter that determines the infarct progression rate and hence the time-point at which recanalization becomes futile is collateral blood supply, which, in turn, is influenced by a number of factors including patient age, pre-existing vascular conditions, as well as other comorbidities (eg, hypertension, hyperglycemia).⁹

So-called fast progressors with poor collateral status are more likely to show completed infarcts before treatment is initiated (and thus do not benefit from recanalization) compared with slow progressors. Noncontrast CT is not able to accurately delineate irreversibly damaged tissue from ischemic tissue that can be salvaged. Advanced imaging methods such as MR imaging and CTP provide additional information on brain tissue hemodynamics over and beyond noncontrast CT and CTA.¹⁰ Of note, CTP provides estimates about tissue viability rather than precise measurements and, therefore, should not be used to exclude patients from treatment in the early time window. However, it undoubtedly contains more information about tissue viability than NCCT and CTA alone. One may, therefore, argue that the depth of ischemia as characterized by CTP imaging findings may be able to explain the discrepancy between technical EVT success (near-complete reperfusion) and poor clinical outcomes. Patients with “deep” and extensive ischemia on CTP maps (large CTP core volumes with low CBV and CBF values compared with the unaffected hemisphere) may not benefit as much from near-complete reperfusion compared with patients with less severe and less extensive ischemia.

If this was the case, CTP would modify the effect of reperfusion on clinical outcomes. In our study, we did not find evidence of such an interaction effect for any of the CTP lesion thresholds tested. In other words, CTP is unlikely to explain the discrepancy between technical EVT success and poor clinical outcomes, perhaps due to the inability of a single CTP threshold to accurately distinguish between irreversibly and reversibly damaged tissue. Because tissue tolerance to ischemia is influenced by many factors including patient and tissue heterogeneity, a single universal CTP threshold (as it is used in clinical practice and hence also in this analysis) seems unlikely to accurately delineate the “true infarct core.”¹¹ In fact, it has been shown that such binary CTP maps often overestimate ischemic changes (“ghost core”).¹²

It has previously been suggested that IV thrombolysis, which is still explicitly recommended in addition to EVT by the current European and North American guidelines,^{2,13} may restore tissue perfusion by dissolving microscopic thrombi in the microcirculation that persist even after macroscopic recanalization has been achieved, thereby exerting a “clearing” effect that improves clinical outcomes.¹⁴ In other words, IV thrombolysis treatment could help to reduce the discrepancy between recanalization success and poor clinical outcomes, though the current study was underpowered to determine whether

such an effect truly exists. Ultimately, the reasons why some patients do poorly despite technical EVT success remain unclear and may include postprocedural complications such as poststroke pneumonia and pulmonary embolism and potentially reduced brain reserve (“brain frailty”) in some patients. The exact underlying reasons and extent to which they contribute to this phenomenon should be investigated in future studies.

Limitations

This study has several limitations. First, we batch-processed perfusion studies from multiple sites with different sequence acquisition settings and CT machines through the RAPID software algorithm, which has introduced some heterogeneity into our data. Second, most of the patient population included in this study presented within 6 hours from onset and, therefore, did not meet guideline-based recommendations for CTP imaging, the latter being restricted to patients in the late window. CTP was simply part of the acute stroke imaging protocol in many participating sites, irrespective of the time of patient presentation. Thus, the generalizability of our results is mostly limited to patients presenting in the early time window. Furthermore, the ESCAPE-NA1 trial was a pragmatic trial that allowed sites to use their locally established imaging protocols, and, thus, no standardization of imaging parameters (eg, section thickness, contrast volume, and so forth) was required, which led to heterogeneity of the available imaging data. Third, just like any randomized trial, the ESCAPE-NA1 trial had rather stringent inclusion and exclusion criteria, and our patient sample is, therefore, not representative of the general EVT population.

CONCLUSIONS

Large baseline CTP lesion volumes are associated with worse outcomes in patients with AIS-LVO undergoing EVT, but CTP does not modify the effect of near-complete reperfusion on clinical outcomes in these patients. Therefore, CTP cannot explain why some patients with LVO have poor outcomes despite near-complete recanalization following EVT.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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