RESEARCH ARTICLE

Incidence, Associations, and Mechanisms of Unexplained Early Neurologic Deterioration After Thrombectomy in Stroke Patients

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Supplementary Material

Background and Objectives

Early neurologic deterioration (END) in ischemic stroke after endovascular thrombectomy (EVT) is a frequent complication that remains unexplained in most cases. We aimed to explore the incidence of, and associated variables with, unexplained END (unEND).

Methods

This is a post hoc analysis of the ESCAPE-NA1 trial, a double-blind, multicentric, randomized clinical trial evaluating nerinetide vs placebo in adult ischemic stroke patients with anterior circulation large vessel occlusion treated with EVT. END was defined as an increase of ≥4 points in the NIH Stroke Scale score between baseline or 2–6 hours after EVT (whichever was the lowest) and 24-hour assessment. The primary outcome was unEND, defined as END without associated hemorrhagic or thrombotic/thromboembolic events. Backward stepwise multivariable logistic regression was used to identify baseline variables independently associated with unEND. In the CT perfusion (CTP) subgroup, regression analysis adjusted for baseline covariates was used to assess the association between unEND and infarct extension beyond the penumbra (IEBP), defined as a follow-up infarct volume larger by at least 10 mL than the initial critically hypoperfused tissue volume (time-to-maximum >6-second volume).

Results

Overall, 1063 patients were included in this study; the median age was 70.8 years (interquartile range 60.7–79.7), and 526 (49.5%) were women. Among them, 172 (16.2%) experienced END: 20 (11.6%) had an associated thrombotic/thromboembolic event, 27 (15.7%) had an associated hemorrhagic event, 8 (4.7%) had both associated thrombotic/thromboembolic and hemorrhagic events, and 117 (68.0%) had an unEND (overall incidence of unEND = 11.0%). Variables independently associated with unEND were anesthesia use (adjusted odds ratio [aOR] 7.23, 95% CI 4.63–11.30), age (aOR 1.02, 95% CI 1.01–1.04 per 1-year increase), and onset-to-reperfusion time (aOR 1.02, 95% CI 1.01–1.03 per 10-minute increase). In patients with available baseline CTP (n = 410), unEND was associated with the presence of IEBP (OR 6.81, 95% CI 2.58–18.01) and larger IEBP volume (OR 1.07, 95% CI 1.01–1.13 per 10-mL increase).

Discussion

UnEND occurred in approximately 10% of large vessel occlusion thrombectomy patients and was associated with older age, longer onset-to-reperfusion time, and anesthesia use. Patients who experienced IEBP, that is, 24-hour infarct volume extension beyond the initial hypoperfused tissue, were 7 times more likely to develop unEND.

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Glossary

ASPECTS = Alberta Stroke Program Early CT Score; **CTP** = CT perfusion; **END** = early neurologic deterioration; **eTICI** = expanded Thrombolysis in Cerebral Infarction; **EVT** = endovascular thrombectomy; **FIV** = follow-up infarct volume; **HI** = hemorrhagic infarction; **IEBP** = infarct extension beyond the penumbra; **IVT** = IV thrombolysis; **LVO** = large vessel occlusion; **mCTA** = multiphase CT angiography; **NCCT** = noncontrast CT; **NIHSS** = NIH Stroke Scale; **Tmax** = time-to-maximum; **unEND** = unexplained END..

Introduction

IV thrombolysis (IVT) and endovascular thrombectomy (EVT) have revolutionized the acute management of ischemic stroke.[1,2] While many patients experience remarkable clinical improvement after EVT, a considerable proportion of patients—ranging from 5% to 20%—develop early neurologic deterioration (END), a complication consistently associated with worse functional outcomes.[3-8] Multiple underlying mechanisms may contribute to END, including hemorrhagic transformation of the infarcted tissue, early ischemic recurrence, malignant edema, seizures, and complications related to EVT (i.e., vessel perforation, embolization in new territory, vasospasm, and contrast neurotoxicity).[4,9-11] However, in more than half of the END cases, the specific mechanisms remain unidentified, a phenomenon referred to as unexplained END (unEND).[7,9]

During ischemic stroke, hypoperfusion of brain tissue below approximately 22 mL/100 g/min leads to an abrupt suppression of cortical electrical activity, causing acute neurologic deficits.[12] Unless reperfusion is achieved swiftly, this cerebral tissue, known as the ischemic penumbra, will invariably progress to infarction at a pace dependent on local perfusion levels.[13,14] Conversely, the surrounding region with mild hypoperfusion, known as benign oligemia, can theoretically remain in the same perfusion state indefinitely without progressing to functional impairment and infarction (i.e., transition to ischemic penumbra and core).[15] Notably, the transition from ischemic penumbra to infarction does not produce new clinical symptoms because there is no functional difference between electrically silent but viable tissue and electrically silent dead tissue.[14] Therefore, it stands to reason that the transition from benign oligemia (asymptomatic tissue) to ischemic penumbra and, ultimately, infarction (symptomatic tissue) probably drives the clinical deterioration in the absence of new thrombotic/thromboembolic or hemorrhagic events (unEND).[9,16]

We aimed to explore the incidence and variables independently associated with unEND in patients with large vessel occlusion (LVO) stroke treated with thrombectomy. Moreover, we aimed to explore the association between unEND and infarct extension beyond the penumbra (IEBP), defined as a follow-up infarct volume that is at least 10 mL larger than the initial critically hypoperfused tissue.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Ethics approval was obtained from the relevant ethics committees at all participating centers, and regulatory approval was obtained as necessary. Written informed consent was provided by patients or their authorized representatives.

Patient Sample

This study is a secondary post hoc analysis of the ESCAPE-NA1 trial, a randomized, multicentric, placebo-controlled, double-blind clinical trial exploring the efficacy and safety of nerinetide in ischemic stroke patients with large vessel occlusion treated with EVT. The inclusion criteria and methodology of the study have been previously published.[17] In brief, inclusion criteria were as follows: (1) adult patients with ischemic stroke; (2) anterior circulation large vessel occlusion (middle cerebral artery or intracranial internal carotid artery); (3) baseline NIH Stroke Scale (NIHSS) score ≥6; (4) baseline functional independence (Barthel Index score >90); (5) ≤12 hours elapsed from time last known well to randomization; (6) Alberta Stroke Program Early CT Score (ASPECTS) ≥5; and (7) moderate-to-good collaterals defined as pial collateral filling of ≥50% of the middle cerebral artery territory on multiphase CT angiography (mCTA). The clinical severity of stroke was assessed with the NIHSS score at baseline, 2–6 hours after EVT, and 24 hours after EVT. For this study, we included all patients with available baseline and 24-hour NIHSS scores, as well as 24-hour imaging follow-up. For a subgroup analysis, we included only patients with available baseline CT perfusion (CTP) and 24-hour infarct volume.

Imaging Acquisition and Analysis

An independent imaging core laboratory blinded to clinical variables, treatment allocation, and outcomes read all neuroimages. Every patient was investigated at baseline with noncontrast CT (NCCT) and mCTA. Baseline imaging parameters of interest included baseline ASPECTS,[18] collateral status evaluated by comparing pial vessel filling and extension on mCTA,[17] and recanalization evaluated on the final intracranial catheter angiography runs using the expanded Thrombolysis in Cerebral Infarction (eTICI) scale.[19] Successful reperfusion was defined as eTICI score ≥2b, poor reperfusion as eTICI score 1–2a, and no reperfusion as eTICI

score 0. Each patient underwent NCCT or MRI 24 hours after receiving acute treatment. Intracranial hemorrhages after reperfusion therapies were classified according to the Heidelberg Bleeding Classification. Hemorrhagic transformation of infarcted tissue was defined as scattered small petechiae with no mass effect (hemorrhagic infarction [HI]-1), confluent petechiae with no mass effect (HI-2), hematoma within infarcted tissue occupying <30% of infarction volume with no substantial mass effect (PH-1), and hematoma within infarcted tissue occupying >30% of infarction volume with obvious mass effect (PH-2).[20] Remote PH was defined as any intraparenchymal hemorrhage remote from the infarcted brain tissue. Intracranial hemorrhages were visually assessed on 24-hour follow-up imaging by 2 expert neuroradiologists (M.G. and J.M.O.) with 24 and 4 years of experience, respectively (detailed methodology published previously).[21] The 24-hour follow-up infarct volume (FIV) was assessed through manual planimetric measurements at 24-hour follow-up axial NCCT or diffusion-weighted MRI by 2 expert neuroradiologists (M.G. and J.M.O.) using the open-source software ITK-SNAP,[22,23] as described in detail previously.[24] Infarcts in a new territory were defined as infarct lesions identified on 24-hour follow-up imaging outside the distal target of the LVO territory.[25]

CTP Imaging Acquisition and Analysis

CTP was performed at a subgroup of participating sites according to local imaging protocols and postprocessed using RAPID perfusion software version 5.2.2 (iSchemaView, Inc., Menlo Park, CA). CTP parameters of interest included ischemic core volume (defined as volume with relative cerebral blood flow <30%), ischemic penumbra (defined as time-to-maximum enhancement [Tmax] >6-second volume minus ischemic core volume), critically hypoperfused tissue (Tmax >6-second volume), and hypoperfusion intensity ratio (defined as the proportion between Tmax >6-second volume and Tmax >10-second volume). IEBP was defined as a follow-up infarct volume that is at least 10 mL larger than the initial critically hypoperfused tissue (FIV − [Tmax >6-second volume] ≥10 mL) (Figure 1). IEBP was also evaluated as a continuous variable, that is, IEBP volume (in milliliters). Hereby, negative values of IEBP volume were imputed as zero.

Possible Causes of END

END was defined as an increase of at least 4 points in the NIHSS score between either (1) baseline or (2) 2–6 hours after EVT (whichever was the lowest) and 24-hour assessment. Whenever 2–6 hour post-EVT NIHSS score was missing, only baseline NIHSS score was considered. This approach aimed to capture all neurologic deterioration, including immediate, persistent worsening after EVT or subsequent decline after initial improvement. Possible causes of END were categorized into 3 groups:

1. END associated with hemorrhagic events: defined as the presence of a hemorrhagic transformation of infarcted tissue (PH-1 or PH-2), remote PH, or subarachnoid hemorrhage secondary to vessel perforation.
2. END associated with thrombotic/thromboembolic events: defined as the presence of infarct in a new territory.
3. END associated with both thrombotic/thromboembolic and hemorrhagic events.
4. unEND: END in the absence of the 2 conditions mentioned above.

Outcomes

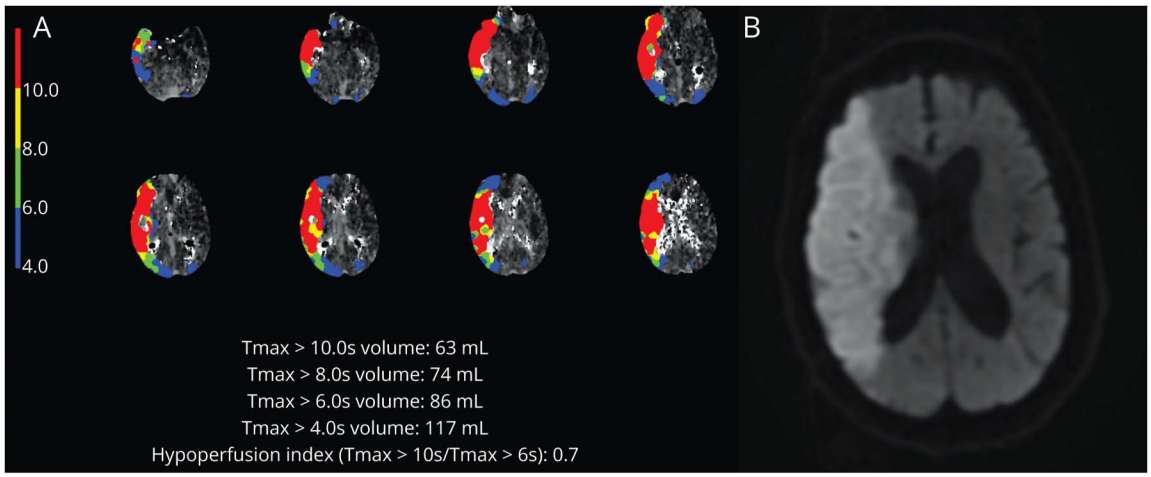
The primary outcome was unEND. Secondary outcomes included overall END, END associated with hemorrhagic events, and END associated with thrombotic/thromboembolic events.

Statistical Analysis

Continuous variables were expressed as medians and interquartile ranges (IQRs) while the categorical variables were reported as counts and percentages. Baseline clinical, radiologic, and therapeutic workflow characteristics, as well as outcomes, were described and compared between patients who experienced unEND and those who did not. Univariable comparisons were made using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for ordinal and continuous variables. Baseline characteristics with p value <0.20 in univariable comparisons were entered in a backward stepwise, multivariable logistic regression model with the outcome as a dependent variable using a removal criterion of p value >0.05. Continuous characteristics were incorporated into the modeling using restricted cubic splines to account for possible nonlinear associations. Effect size estimates derived from logistic regression analyses were reported as adjusted odds ratios (aORs) with 95% CIs. The ORs reported in this study represent the odds ratios on the outcome for the presence of a given baseline characteristic (e.g., history of hypertension) vs its absence (e.g., no history of hypertension), with the latter serving as the reference category. In the case of continuous and ordinal variables as baseline characteristics, the OR reported represents the odds ratio on the outcome for a 1-unit increase. Because the data are from a randomized clinical trial testing nerinetide, we investigated whether nerinetide administration was associated with unEND after adjusting for baseline covariates associated with the outcome in the multivariable analyses.

The second part of the analysis was conducted only in patients with available baseline CTP (eMethods). The same main analyses performed in the overall sample were repeated. The association between IEBP and unEND was assessed using logistic regression analyses. Patients with END associated with thrombotic/thromboembolic or hemorrhagic events were excluded from the IEBP analysis because the new ischemic stroke or parenchymal hematoma would distort 24-hour infarct volumes and interfere with IEBP calculations. Indeed, if a patient experiences END associated with thrombotic/thromboembolic or hemorrhagic events, the infarct volume measured at 24 hours is no longer solely the result of the progression of initial hypoperfused tissue—which is the phenomenon of interest in our analysis—yet it reflects both the original ischemic lesion

Figure 1 Exemplary Case of Unexplained END With IEBP



A patient presented with an occlusion of the distal M1 segment of the right middle cerebral artery. The baseline NIHSS score was 13, with a tissue at risk (Tmax >6 seconds) of 86 mL (A). Thrombectomy was attempted under conscious sedation but was unsuccessful (eTICI = 0). At 24 hours, the clinical reassessment revealed a worsened NIHSS score of 24 while the follow-up revealed an infarct volume of 210 mL on diffusion-weighted MRI (B), corresponding to an IEBP volume of 124 mL. eTICI = expanded Thrombolysis in Cerebral Infarction; IEBP = infarct extension beyond the penumbra; NIHSS = NIH Stroke Scale.

and the new ischemic/hemorrhagic lesion. Moreover, the IEBP subanalysis was limited to patients who experienced deterioration from baseline (time of CTP acquisition) to 24 hours. This means that individuals who experienced a worsening of the NIHSS score at 24 hours compared with after EVT, but not compared with baseline, were excluded from this analysis. This is because CTP imaging was acquired only before EVT, and these perfusion parameters are likely not informative of the perfusion status of the patients after EVT (because, arguably, the critically hypoperfused volume significantly decreased after EVT).

Because cerebral edema can grow by up to 30 mL between baseline noncontrast CT and 24-hour contrast CT in patients with large core stroke,[26] we performed a sensitivity analysis defining IEBP as a follow-up infarct volume that is at least 30 mL larger than the initial critically hypoperfused tissue (FIV − [Tmax >6-second volume] ≥30 mL).

All calculated p values were 2-tailed. Statistical significance was assumed at $p < 0.05$. The statistical analysis was performed with Stata (version 18.0).

Data Availability

The corresponding author will provide access to the data underlying this analysis on reasonable request and after approval by the ESCAPE-NA1 executive committee.

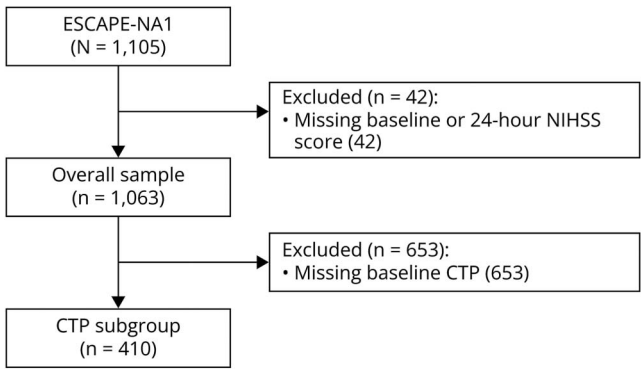
Results

Patient Characteristics, END Incidence, and Possible Causes in the Overall Sample

Of 1105 patients enrolled in ESCAPE-NA1, 42 were excluded because of a missing 24-hour NIHSS evaluation; thus, 1063 patients were included in this analysis (Figure 2). The median age was 70.8 years (IQR 60.7–79.7), and 526 (49.5%) were female. A total of 172 patients (16.2%) experienced END: 20 (11.6%) had an associated thrombotic/thromboembolic event, 27 (15.7%) had an associated hemorrhagic event, 8 (4.7%) had both associated thrombotic/thromboembolic and hemorrhagic events, and 117 (68.0%) presented an unEND (overall incidence of unEND = 11.0%) (Figure 3).

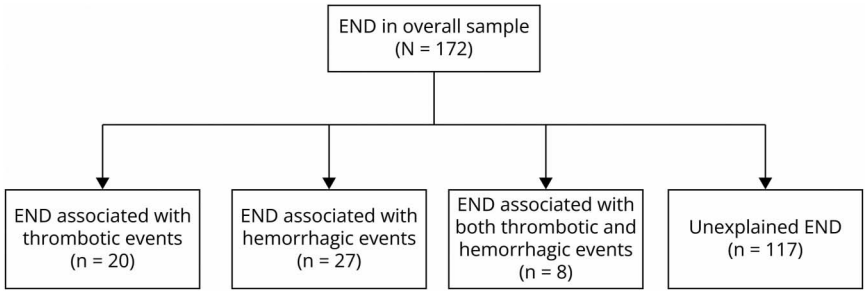
Patients who experienced unEND, compared with those who did not, were older (median 74.7 years [IQR 62.2–82.5] vs 70.5 years [IQR 60.6–79.2]; $p = 0.019$); had higher admission systolic blood pressure (152 mm Hg [IQR 134–167] vs 145 mm Hg [IQR 130–167]; $p = 0.048$); had worse final reperfusion status (eTICI = 0 [13.9% vs 3.5%], eTICI = 1–2a [11.3% vs 7.0%], and eTICI ≥2b [74.8% vs 89.5%]; $p < 0.001$);

Figure 2 Study Workflow



CTP = CT perfusion; NIHSS = NIH Stroke Scale.

Figure 3 Flowchart of the Incidence of the Possible Causes of END in the Overall Sample



END = early neurologic deterioration.

and more frequently used anesthesia (no sedation [7.9% vs 23.2%], conscious sedation [46.5% vs 64.4%], and general anesthesia [45.6% vs 12.4%]; $p < 0.001$). Table 1 summarizes the demographics, medical history, clinical factors, treatment, and workflow in patients with and without unEND.

Variables Independently Associated With unEND in the Overall Sample

In the overall sample, in a multivariable regression analysis, the variables independently associated with unEND were anesthesia use (aOR 7.23, 95% CI 4.63–11.30), age (aOR 1.02, 95% CI 1.01–1.04 per 1-year increase), and onset-to-reperfusion time (aOR 1.02, IQR 1.01–1.03 per 10-minute increase) (Table 2). When anesthesia was included in the multivariable model as a factorial independent variable, the aORs were 3.04 (95% CI 1.06–8.75) for conscious sedation and 26.95 (95% CI 9.35–77.68) for general anesthesia.

In a multivariable regression analysis adjusted for age, anesthesia use, and onset-to-reperfusion time, we observed no association between nerinetide administration and unEND (aOR 0.84, 95% CI 0.52–1.35).

Patient Characteristics, Incidence, Possible Causes, and Variables Independently Associated With unEND in the CTP Subgroup

Of 1066 patients in the overall sample, 410 were investigated with baseline CTP and were included in the CTP sample (Figure 2). The differences in baseline characteristics and workflow variables between patients who did and did not undergo baseline CTP in ESCAPE-NA1 have been published and discussed in a previous article,[27] with significant differences noted in systolic blood pressure, atrial fibrillation, interhospital transfer rates, and general anesthesia use between the 2 groups.

In the CTP subgroup, in a multivariable regression analysis, the variables independently associated with unEND in the CTP subgroup were previous stroke/TIA (aOR 2.69, 95% CI 1.21–6.00), anesthesia use (aOR 2.13, 95% CI 1.09–4.16), and final reperfusion status (aOR 0.65, 95% CI 0.50–0.83) (eTables 1–3).

Association Between IEBP and unEND

After excluding patients with END associated with thrombotic/thromboembolic or hemorrhagic events, patients who experienced unEND (defined as clinical deterioration between baseline and 24 hours), compared with patients who did not, more frequently developed IEBP (50% [n = 9] vs 12.9% [n = 48]; $p < 0.001$) and the IEBP volume was significantly larger (15.7 mL [IQR 0–64.9] vs 0 mL [IQR 0–0]; $p < 0.001$). There was a significant association between unEND and the presence of IEBP (OR 6.81, 95% CI 2.58–18.01) and IEBP volume (OR 1.07, 95% CI 1.01–1.13 per 10-mL increase) (Figure 4). Results were similar in the sensitivity analysis with IEBP defined as an increase of at least 30 mL (FIV – [Tmax >6-second volume] ≥30 mL) (Supplementary Materials).

Discussion

The key findings of our study were as follows: (1) approximately 1 in every 10 patients experienced unEND; (2) older age, anesthesia use, and longer time from onset to reperfusion were independently associated with unEND, and (3) patients with IEBP, defined as a follow-up infarct volume larger than the initial critically hypoperfused tissue by at least 10 mL, were nearly 6 times more likely to develop unEND.

The overall proportion of patients with END in our study was 16.2%, which is well within the range of studies that reported END proportions in EVT-treated stroke patient samples between 5% and 20%.[4,5,7,8,11] Different END definitions and population characteristics—such as occlusion location, anesthesia use, and imaging selection criteria—likely contributed to the observed differences in the proportions of patients with END across these studies. In line with previous thrombectomy studies, we found that more than half of END cases were not associated with hemorrhagic or thrombotic/thromboembolic events (unEND).[4,5,7,8,11] The actual cause of END can be challenging to determine with certainty, and possibly, multiple causes contribute simultaneously to some cases.[3] Therefore, we refer to associated events rather than causes in this study. The categorization of the causes and the resulting definitions of unEND are also widely heterogeneous across studies.[3-5,7,8,11]

Table 1 Patient Characteristics in unEND and No unEND Groups in the Overall Sample

	unEND (n = 117)	No unEND (n = 946)	*p* Value
Demographics and medical history			
Age, y, median (IQR)	74.7 (62.2–82.5)	70.5 (60.6–79.2)	0.019
Sex, female, n (%)	63 (53.9)	463 (48.9)	0.328
Hypertension, n (%)	81 (69.2)	667 (70.5)	0.830
Diabetes, n (%)	27 (23.1)	180 (20.0)	0.441
Previous stroke/TIA, n (%)	22 (18.8)	127 (13.4)	0.121
Coronary artery disease, n (%)	26 (22.2)	218 (23.1)	0.908
Clinical factors			
Witnessed stroke onset, n (%)	69 (59.0)	540 (57.2)	0.767
Baseline NIHSS score, median (IQR)	18 (13–21)	17 (12–21)	0.481
Admission systolic blood pressure, mm Hg, median (IQR)	152 (134–167)	145 (130–163)	0.048
Admission diastolic blood pressure, mm Hg, median (IQR)	80 (74–92)	80 (70–90)	0.322
Blood glucose, mmol/L, median (IQR)	6.9 (6.0–8.8)	6.7 (5.9–7.8)	0.066
Baseline ASPECTS, median (IQR)	8 (7–9)	8 (7–9)	0.825
Occlusion site ICA, n (%)	25 (21.4)	175 (18.5)	0.453
Good collateral status, n (%)	24 (20.7)	159 (17.0)	0.064
Treatment and workflow			
IV thrombolysis, n (%)	68 (58.1)	563 (59.5)	0.766
IV nerinetide, n (%)	56 (47.9)	472 (49.9)	0.696
Interhospital transfer, n (%)	65 (55.6)	555 (58.7)	0.551
Final reperfusion status[a]			<0.001
No reperfusion (eTICI = 0), n (%)	16 (13.9)	33 (3.5)	
Poor reperfusion (eTICI = 1–2a), n (%)	13 (11.3)	66 (7.0)	
Successful reperfusion (eTICI ≥2b), n (%)	86 (74.8)	843 (89.5)	
Onset-to-reperfusion time, min, median (IQR)	256 (180–352)	223 (159–344)	0.045
Anesthesia use[a]			<0.001
None, n (%)	9 (7.9)	219 (23.2)	
Conscious sedation, n (%)	53 (46.5)	607 (64.4)	
General sedation, n (%)	52 (45.6)	117 (12.4)	

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; CTA = CT angiography; CTP = CT perfusion; END = early neurologic deterioration; eTICI = expanded Thrombolysis in Cerebral Infarction; HIR = hypoperfusion intensity ratio; ICA = internal carotid artery; IQR = interquartile range; NCCT = noncontrast CT; NIHSS = NIH Stroke Scale; unEND = unexplained END.
[a] Available in 943 of 946 patients with no END and 114 of 117 with END.

Of note, we did not consider reperfusion failure as an explanation for END because the transformation of ischemic penumbra into infarction does not explain a clinical deterioration.[12,14,28]

We identified older age, use of anesthesia, and longer time from onset to reperfusion as variables independently associated with unEND. Age and time to reperfusion are widely recognized as critical, outcome-determining factors in ischemic stroke.[29,30] The use of general anesthesia has also been reported in previous studies to be associated with worse outcomes.[31] In our sample, both general anesthesia and conscious sedation were significantly associated with unEND; yet, the effect size was substantially greater for general anesthesia, suggesting a potential stepwise relationship between increasing levels of sedation and the risk of unEND. Besides

Table 2 Multivariable Analysis of Independent Predictors of unEND in the Overall Sample

Predictors	Adjusted OR (95% CI)
Anesthesia use	7.23 (4.63–11.30)
Age (per 1-y increase)	1.02 (1.01–1.04)
Onset-to-reperfusion time (per 10-min increase)	1.02 (1.01–1.03)

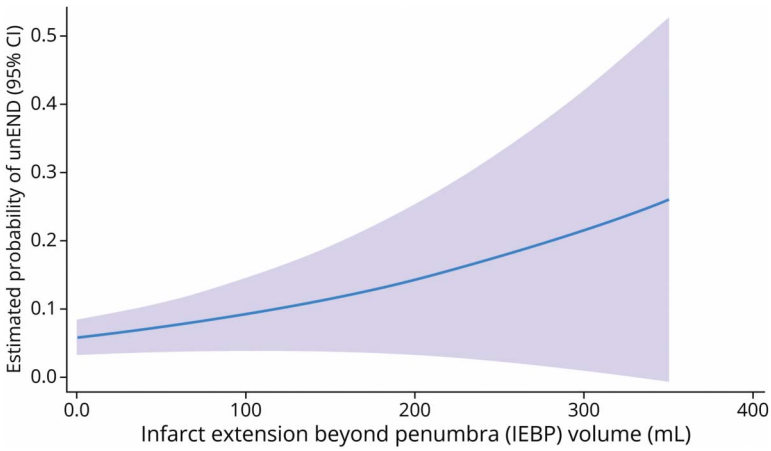
Abbreviations: NIHSS = NIH Stroke Scale; OR = odds ratio; unEND = unexplained early neurologic deterioration.
Other variables considered, but excluded by the backward stepwise multivariable logistic regression model, were previous stroke, admission systolic blood pressure, blood glucose levels, good collateral status, and final reperfusion status.

a possible causal relationship with outcomes, general anesthesia may indirectly reflect a worse overall patient status or influence the 24-hour clinical evaluation because of the prolonged time needed to eliminate the anesthetic drugs in some patients.[4,11] In contrast to our findings, previous studies have identified baseline blood glucose levels, NIHSS score, collateral status, and number of EVT passes as independent predictors of unEND.[4,5,7] The observed discrepancy may be attributed to differences in the study population and methodology.

In the subgroup analysis of patients with baseline CTP, we showed that IEBP—defined as a follow-up infarct volume larger than the initial critically hypoperfused tissue by at least 10 mL—was observed in half of the unEND cases. The risk of unEND increased by approximately 7% for every 10-mL IEBP volume increase, and the presence of IEBP increased the risk of unEND by almost sevenfold. Our findings are in line with those of a previous study that reported follow-up infarct beyond the boundaries of the penumbra tissue in 9 of 10 cases of unEND after IVT, with the new infarct regions roughly corresponding to the topography of the new neurologic deficits.[10] Although exploratory and based on small samples, these results collectively support the hypothesis that unEND might be driven by the transition from benign oligemia (asymptomatic tissue) to ischemic penumbra (symptomatic tissue) and, ultimately, infarction. The perfusion window at which benign oligemia occurs is wide and varies among patients, ranging from 22 to 50 mL/100 g/min.[14,15] Therefore, a benign oligemia zone critically close to the ischemic penumbra threshold likely exists (i.e., between 22 and 30 mL/100 g/min)—"vulnerable oligemia." While the underpinning biological processes that promote this transition remain unclear,[9] potential mechanisms include (1) changes in thrombus characteristics or systemic blood pressure leading to decreased local perfusion,[10] (2) alterations in systematic factors that affect tissue resilience to ischemic damage (i.e., blood glucose levels or oxygen saturation),[9,10,32] and (3) spreading ischemia mediated by spreading depolarization.[33,34]

Our study has some limitations. First, the underlying causes of END are often unclear, and no consensus on classification has been established to date. However, we used a conservative measure of unEND, which more likely may have led to an underestimation, not overestimation, of the true proportion of patients with unEND. Second, the 24-hour NIHSS score might not fully capture fluctuations in neurologic status, and the 4-point increase criterion is somewhat arbitrary. Third, not all patients underwent MRI as follow-up imaging, which is more sensitive than NCCT to detect small ischemic lesions.

Figure 4 Association Between IEBP Volume and Unexplained END in the CTP Subgroup



CTP = CT perfusion; END = early neurologic deterioration; IEBP = infarct extension beyond the penumbra.

While most of the missed lesions were likely too small to result in a 4-point increase on the NIHSS, it is conceivable that small lesions located in particularly eloquent areas, such as the corticospinal tracts, could have led to such an outcome. Fourth, baseline CTP was available only in a subgroup of patients, limiting the generalizability of our findings. Fourth, IEBP might have occurred in other patients with END or patients with a smaller (<4-point) increase in the NIHSS score, suggesting that the clinical deterioration driven by IEBP may be underestimated. Fifth, our definition of IEBP might, in part, reflect the inaccuracy of the CTP threshold for ischemic penumbra (Tmax >6 seconds) rather than an actual extension. However, the robust association with clinical deterioration suggests that some degree of hypoperfusion lesion extension has likely occurred. Sixth, early cerebral edema formation may have contributed to IEBP in some patients. However, results were similar in a sensitivity analysis where we defined IEBP as an increase of at least 30 mL between critical hypoperfused tissue and follow-up infarct volume. Finally, other possible causes of END, such as seizures and metabolic disturbances, were not systemically evaluated in our sample.

In our study, unEND occurred in approximately 10% of patients with LVO stroke treated with thrombectomy and was associated with older age, longer onset to recanalization time, and general anesthesia use. Patients who experienced IEBP, that is, those with 24-hour infarct volume extended beyond the initial hypoperfused tissue at risk, were approximately 7 times more likely to develop unEND. unEND might be driven by the transition from benign oligemia (asymptomatic tissue) to ischemic penumbra (symptomatic tissue) and, ultimately, infarction in a cerebral zone where perfusion values are initially within the oligemic range but critically close to the penumbra threshold—"vulnerable oligemia."

Author Contributions

U. Pensato: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S.B. Coutts: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B. van Adel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. R. Chapot: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. V. Puetz: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Demchuk: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Goyal: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.D. Hill: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.M. Ospel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Disclosure

M. Goyal reports personal fees from Medtronic, Stryker, Microvention, and Mentice, during the conduct of the study; unrestricted research grants to the University of Calgary from NoNO, Stryker, and Medtronic; patents for a system of acute stroke diagnosis, with royalties paid to GE Healthcare, and a system of simulation for acute neurointervention, with royalties paid to Mentice; and ownership interest in Circle Neurovascular. M.D. Hill reports grants from the Canadian Institutes for Health Research, Alberta Innovates, and NoNO, for the conduct of the study; reports personal fees from Merck; reports non-financial support from Hoffmann-La Roche Canada; reports grants from Covidien (Medtronic), Boehringer-Ingleheim, Stryker, and Medtronic, outside the submitted work; reports a patent for systems and methods for assisting in decision-making and triaging for acute stroke patients, issued to US Patent office Number 62/086,077; owns stock in Calgary Scientific; is a director of the Canadian Federation of Neurological Sciences and Circle Neuro-Vascular; and has received grant support from Alberta Innovates Health Solutions, CIHR, Heart & Stroke Foundation of Canada, and the National Institute of Neurological Disorders and Stroke. J.M. Ospel is a consultant for Abbvie and Nicolab. All other authors declare no competing interests. Go to Neurology.org/N for full disclosures.

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Appendix Coinvestigators

Coinvestigators are listed at Neurology.org.

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