Infarct Progression in the Early and Late Phases of Acute Ischemic Stroke

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Neurology® 2021;97:S60-S67. doi:10.1212/WNL.0000000000012795

Abstract

Purpose of Review
To explore factors associated with infarct progression in the early and late phase of acute ischemic stroke in patients undergoing endovascular therapy.

Recent Findings
Following ischemic stroke, brain injury can progress at a variable rate, at the expense of “penumbral tissue,” which is the ischemic tissue at risk of infarction. Despite dramatic advances in endovascular stroke therapies with early revascularization in more than 80% of cases, nearly half of patients do not achieve functional independence despite successful recanalization. This is largely attributed to the irreversible damage that is already extensive at the time of revascularization.

Summary
The underlying pathophysiology and determinants of the core infarct progression are complex and multifactorial, depending on a balance between brain energy consumption and collateral perfusion supply. It is crucial to develop creative and individualized theranostics to predict infarct progression and to “freeze” the tissue at risk prior to recanalization.
Emergent large vessel occlusion (ELVO) comprises about 30%-40% of acute ischemic strokes and is responsible for 90% of functional loss and 20% mortality in 3 months if left untreated. Endovascular therapy (EVT) is a highly effective treatment that has dramatically affected outcomes following ELVO. The more recent DAWN and DEFUSE-3 trials extended the endovascular treatment window up to 24 hours following symptom onset based on advanced imaging studies. However, a considerable number of patients with stroke with ELVO are not candidates for EVT at the time of presentation due to a large core infarct. Furthermore, about 50% of patients undergoing EVT do not achieve good outcome despite successful recanalization, mainly due to fast progression of penumbral tissue loss. It should also be recognized that some patients achieve favorable outcomes despite large volumes of infarct, whereas some patients develop significant disability despite small infarct volumes. In this paradigm, it is critical to identify factors associated with slow vs fast infarct growth, and to deliver early individualized therapeutics to slow penumbral loss. Thus, large potential exists for creative diagnostics, therapeutics, and ideally, theranostics for ELVO.

Definitions: Fast vs Slow Progressors

It has long been understood that patients with ischemic stroke demonstrate a variable pattern and timing in infarct progression and development of irreversible brain injury, as patients with similar sites of occlusion present with significantly variable core infarct volumes independent of last known well time. On this basis, an intuitive categorization of ELVO has been suggested: 1: fast progressors (patients with large core infarcts despite early presentation [recanalization <6 hours], likely due to failing collaterals); 2: slow progressors (patients with small core infarcts and considerable penumbral tissue despite late presentation beyond 6 hours up to a day, likely due to robust collaterals) (Figure 1). The underlying pathophysiology and determinants of the velocity of infarction are complex and multifactorial, but cumulative evidence suggests that an interplay between energy supply and energy demand in the hypoperfused tissue sets the pace of the infarct growth. Determinants of infarct growth and ischemic tolerance can be broadly categorized as follows: (1) tissue-related factors, including age, baseline metabolic demands, and preexisting brain state, including white matter disease or prior vascular insults, and the cell type under stress (gray vs white matter; neurons vs glial tissue); (2) flow-related factors, such as collateral circulation status, preexisting comorbidities affecting collateral robustness such as diabetes or vascular stenoses, perfusion pressure, blood oxygen content, and cerebral edema in the area of ischemia; (3) occlusion-related factors, such as site of occlusion, and complete vs partial obstruction of the vessel; and (4) individual variations, including the interindividual (e.g., genetic factors associated with collateral circulation development, demographics such as age and sex, premorbid vascular risk factors and stenoses, and ischemic conditioning) and intra-individual (e.g., location of vascular occlusion and blood pressure variability) heterogeneity that can modulate the velocity of infarct growth. It is also important to consider differential ischemic tolerance of various CNS components (including neurons, astrocytes, microglia, oligodendrocytes, and endothelial cells). Each of these components may be differentially affected by the ischemic process, which may have implications for recovery and long-term functional and cognitive outcomes.

Infarct Growth Pattern in Brain

Previous studies have suggested that infarct growth is variable early after stroke. Using diffusion and perfusion MRI in 8 adult monkeys with transfemoral middle cerebral artery (MCA) occlusion, the spatiotemporal evolution of infarcted tissue was found to follow a logarithmic pattern in the earliest hours after stroke. Whereas the infarct growth rate decreases as infarct volume increases, a logarithmic growth function has been proposed to be a more accurate representation of infarct growth as compared to linear models. However, the slope of the growth function could vary widely based on the interplay of different factors such as robustness of collaterals. The effect of collateral status on dynamics of infarct growth was depicted in an interesting experiment, where authors demonstrated that the infarct growth function assumes a linear shape at higher collateral grades and a logarithmic shape at lower collateral grades. Therefore, presence and robustness of collaterals determines the curve on which the infarct growth will lie. Finally, successful revascularization can differentially change the equation at any time point.

In a cohort of 51 patients with successful endovascular recanalization following M1 MCA occlusion presenting <6 hours from onset of symptoms, patients were divided into hyperacute (<1.85 hours) and acute presenters (≥1.85 hours) based on onset to imaging time. The mean Alberta Stroke Program Early CT Score (ASPECTS) difference at 24 hours vs baseline imaging was 2.7 vs 1.6 (p = 0.04) between hyperacute and acute presenters. The authors concluded that a relatively constant imaging to reperfusion time was associated with greater infarct growth in the earliest poststroke hours, suggesting a greater lesion growth dynamic in the hyperacute
Epidemiology: Incidence and Prevalence of Fast vs Slow Progressors

Although infarct progression speed is frequently considered in potential EVT candidates, the incidence and its characteristics are not well-established. In endovascular landmark trials, about 40%–46% of patients with successful reperfusion within 3–6 hours poststroke did not achieve favorable outcomes. These patients represent the fastest progressors, benefiting from the earliest possible revascularization.

The incidence of slow progressors is also not well-established, ranging from ≤30% to 30%–50% of anterior circulation ELVO patients in randomized trials. However, these estimates were based on data from patients selected for EVT in earlier time windows only. Furthermore, an important limitation of clinical studies investigating infarct growth progression is lack of differentiation between actual stroke onset and the last known well time. Most prior studies are based on last known well time, which may not be a real surrogate for actual ischemic onset for modeling stroke progression. In a study by Rocha et al., the authors used the following criteria to define slow and fast progressors in patients with acute stroke.
presenting to a comprehensive stroke center: fast progressors: ischemic core >70 mL in the early 0–6 hours after stroke onset; slow progressors: patients with ischemic core ≤30 mL in the delayed epoch after stroke onset (>6–24 hours). Authors used the automated RAPID software to measure the ischemic core volume using CT perfusion. In this study, 25% of patients had an ischemic core >70 mL in the early epoch (fast progressors), whereas 55% of patients had an ischemic core ≤30 mL in the delayed epoch (slow progressors). Interestingly, fast progressors were the most prevalent group (in 3–4.5 hours window), whereas the rate of slow progressors was not statistically different across 4.5-hour intervals of the delayed epoch. It was concluded that fast progressors represented 1 of 4 patients with ELVO during the early epoch and 40% of cases between 3 and 4.5 hours.

**Pathophysiology: Underlying Mechanism of Infarct Progression**

Ischemic thresholds have been identified from models of ischemic stroke. The speed of neural loss in ischemic tissue is associated with blood flow, with values <10 mL/100 g/min resulting in neuronal loss.

The underlying mechanism of fast and slow progressors following ELVO is unclear. It is known that the infarct growth rate during ELVO is a function of robustness of collaterals and the interplay between multiple factors, including physiologic parameters such as genetic background, age, demographics, acquired comorbidities, blood pressure variability, head position, CO2, temperature, and blood glucose, linked to the leptomeningeal collateral blood flow. The robustness of collaterals is affected by factors such as age, blood pressure variability, and other physiologic parameters. Presenting blood sugar has also been found to be associated with infarct growth and collateral flow.

**Characteristics of Collateral Circulation**

Collateral network consists of extracranial to intracranial connections, circulation at the circle of Willis, as well as pial and leptomeningeal collaterals. During ELVO, the collateral network would include a supplying artery, for example, branches from anterior or posterior cerebral artery contributing antegrade flow to an ischemic MCA territory.

**Genetic Factors**

There is a variability in tissue resistance to reductions in blood flow that may in part be influenced by the genetic background. Zhang et al. reported variability in the number and size of leptomeningeal collaterals across mice attributable to genetic factors. In another study, with MCA occlusion in mice, C57BL/6 J mice (good pial collaterals) had smaller infarct volumes than the BALB/c mice (poor pial collaterals). A single nucleotide polymorphism of the Rubeap2 gene is reported to be associated with almost 80% of variability in pial collateral characteristics in mice, and this is being tested for confirmation in human studies. The multicenter Genetic Determinants of Collateral Status in Stroke (GENEDCSS) study is in progress to evaluate this hypothesis.

**Pressure Gradient and Vasoreactivity**

Theoretically, the function and capacity of the retrograde leptomeningeal blood flow during ELVO depends on 2 main factors: the pressure gradient and the leptomeningeal arterioles (resistance in collateral vasculature network), as well as the integrity of the regional cerebral autoregulation during ELVO. The intrinsic distensibility of the anastomotic leptomeningeal arterioles is an important factor that allows for redistribution of flow into the ischemic territory. Even subtle increases in leptomeningeal vascular diameter in animal models of MCA occlusion would exponentially increase the collateral flow. Clinically, this is consistent with prior findings of an association between elevated blood pressures and poor collateral grades in ELVO strokes. This can be explained considering that chronic hypertension would result in an elevated collateral vasculature tone. Future studies will need to identify factors influencing arterial reactivity in pial collateral circulation. Another factor that can play an inconsistent role in the robustness of collaterals is the presence of cerebrovascular arterial stenoses. In general, gradual occlusion such as moyamoya syndrome or ICA occlusion allows compensatory collateral flow and better collaterals. Similarly, it has been shown that individuals with significant ICAD have an enhanced collateral supply based on CT perfusion imaging. On the other hand, mild to moderate intracranial stenosis has been shown to have an inverse relationship with the degree of pial collaterals.

**Edema**

Brain edema is another pathophysiologic explanation for early loss of collateral supply in ELVO. Prior animal studies have reported edema and an increased volume of water content in ischemic tissue 1–3 hours following an MCA occlusion. Long ago, Symon et al. reported that increased water content in ischemic tissue was responsible for extension of infarct region. Thus, elevated interstitial pressure and increased resistance in collateral vascular network secondary to the cerebral edema is another pathophysiologic mechanism for perpetuating the penumbral tissue hypoperfusion. This likely represents a cycle where ischemia promotes edema and early cerebral edema leads to decreased perfusion and worsening of the edema. Future creative therapeutic approaches can target reducing early edema in early settings after symptom onset.

**Diagnostics: Imaging Tools to Assess Collaterals**

The status of a collateral network is the only available biomarker for prediction of infarct volume and outcomes following stroke. A robust means for estimation of collateral status is multiphase CT angiography (CTA). Prior research has validated various collateral measurement scales using single-phase CTA scores based on the maximum intensity projection images, where higher scores have been associated with a lower final core volumes and better clinical outcomes (Figure 2). However, the
The efficacy of collateral network can be examined only with perfusion studies (CT and MRI perfusion), which represents effectiveness of the collateral circulation. Ischemic core has been conventionally defined as areas with severely decreased cerebral blood volume or cerebral blood flow. In the absence of perfusion studies, the robustness of collateral flow can be estimated by the discrepancy of the parenchymal imaging and clinical symptoms (small infarct size despite high scores on the National Institutes of Health Stroke Scale). A variety of ischemic core and penumbra thresholds have been used, which have been neither standardized nor validated. For instance, software-induced differences in CTP-derived core measurements using identical source data are as high 23 mL. It has also been shown that the current thresholds for the CTP maps could overestimate the ischemic core, that is, the “ghost core” concept, resulting in exclusion from reperfusion therapies in some patients. Because tissue tolerance to ischemia is influenced by many factors, including patient and tissue heterogeneity, as discussed above, a single unique perfusion core infarct threshold measure may not be accurate. Future research is warranted to better characterize the optimal biomarkers for reversible vs irreversible ischemic injury tailored into each patient’s imaging and clinical phenotype from symptom onset to treatment.

**Therapeutics: Penumbral Protection in the Era of EVT**

Endovascular thrombectomy has introduced the new paradigm of reliable recanalization and increased likelihood of penumbral salvage. The idea is to use strategies to buy time with minimizing the core volume growth prior to recanalization, thereby improving outcomes following recanalization or making more patients eligible for reperfusion therapies.

Mechanisms for the penumbral protection prior to or during thrombectomy are proposed based on reducing the energy demand of the tissue or by enhancing the energy delivery to the ischemic tissue via enhancing the collaterals and blood flow. Various pharmacologic and nonpharmacologic interventions have been proposed to achieve this goal. Most of the nonpharmacologic interventions are noninvasive and easy to administer and could potentially be delivered in the field (Table).

**Improving Oxygen Supply to the Penumbra**

Hyperbaric oxygen therapy has shown efficacy in animal experimental models, but translational clinical studies were largely negative. An alternative more real-world feasible strategy includes normobaric hyperoxia using normobaric oxygen therapy with or without perfluorocarbons. Perfluorocarbons are chemicals with large oxygen-carrying capacity that can be administered intravenously and can enhance the effects of inhaled oxygen.

Two prior clinical trials have demonstrated the feasibility and safety of normobaric hyperoxia but have failed to show clinical benefit. However, no trial has investigated the new paradigm of clinical benefit in the prerecanalization stage in ELVO.

**Collateral Optimization**

Enhancement of collaterals at the hyperacute phase following ELVO has 2 sides. First, a growing body of evidence suggests that good collateral flow can significantly increase the likelihood of successful recanalization with IV or intraarterial thrombolysis. Second, collateral optimization can reduce the progression of infarction prior to recanalization. Intrinsically and extrinsically factors
associated with efficacy and recruitment of collateral vessels were reviewed above. Several interventions such as enhancement of cerebral blood flow have been explored over the past few decades with inconsistent results. Inconsistencies could be attributed to lack of personalization of such treatment tailored the patient profile. It is important to recognize that ELVO has turned into a new disease paradigm given the potential availability of relatively reliable recanalization. This represents a new opportunity to re-explore the abandoned therapeutic modalities, as well as newer neuroprotective therapies to slow down the tissue infarct as early as the onset of ischemia.

**Clinical Effect of Collaterals on Successful Recanalization**

In 92 patients with ELVO in the 6 hours window, the efficacy of thrombolytic therapy was strongly associated with the robustness of collateral network. In another study using MRI, the robustness of collateral circulation was significantly associated with successful recanalization rates. Furthermore, successful recanalization in the absence of good collaterals was associated with significantly greater infarct volume growth after intervention.

**Cerebral Blood Flow Augmentation**

Cerebral blood flow (CBF) augmentation with treatments that contribute to a volume expansion or with induced hypertension have been previously studied decades ago. This process is thought to be mediated at various levels such as the neurons, the cerebral connective tissue, and the blood vessels. Hypothetically, agents with vasodilatory effects could potentially augment blood flow to the ischemic tissue via collaterals. In addition to vasodilation, methylxanthine derivatives such as pentoxifylline are implicated in the inhibition of platelet aggregation. Prior studies that tested these agents are outdated and underpowered and did not evaluate the infarct growth rate with respect to collateral status.

Induced hypotension in animal models has been shown to result in worsening neurologic deficit that was reversible with increased blood pressure. An observational study in adults admitted to the intensive care unit with acute stroke have suggested that continuous nicardipine use was associated with worse clinical outcomes. As such, despite limited data about induced hypertension, it represents a therapeutic intervention that is sometimes used for ELVO and has a physiologic basis. Therefore, this remains one of the areas of uncertainty as the role of blood pressure and the nature of blood pressure modulation (vasoactive drugs vs hemodynamic response) may be different in different time points during ischemia.

**Remote Ischemic Preconditioning**

This is another strategy to reduce the infarct growth progression and is traditionally applied with limb ischemia. Beneficial effects are attributed to the release of signaling molecules that may enhance collateral circulation, thereby significantly improving CBF and reducing infarct size. Prior clinical trials have not been conclusive, and RESCUE, an ongoing phase IIb trial, is currently investigating the role of leg ischemia within 6 hours of stroke onset in patients receiving intraarterial or IV thrombolysis.

**Transient Descending Aortic Balloon Occlusion**

Temporary balloon occlusion of the abdominal aorta has been shown to increase perfusion pressure in intracranial circulation and can improve penubral perfusion in ischemic states. Another approach includes electrocardiogram-gated external counterpulsation that involves the use of pressure cuffs in lower limbs that are inflated at high pressures to induce retrograde flow in the abdominal aorta. Widespread implementation of these therapeutics is limited by lack of sufficient clinical and preclinical data as well as insufficient technological development.

**Neurogenic Modulation of CBF**

Sphenopalatine ganglion stimulation (SPGS) activates the parasympathetic innervation of the cerebral vessels, which in turn results in vasodilation and increased blood flow. This requires placement of a small electrode through the oral cavity

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**Table** Potential Interventions to Freeze Penumbral Loss and Slow Infarct Progression

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<thead>
<tr>
<th>Pharmacologic approach</th>
<th>Nonpharmacologic approach</th>
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<tr>
<td>Reduction of peri-infarct depolarizations/intrinsic neuroprotection</td>
<td>Increase collateral flow</td>
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<tr>
<td>NA-1</td>
<td>Induced hypertension</td>
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<td>PSD95 inhibition</td>
<td>Sphenopalatine ganglion stimulation</td>
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<td>Ketamine</td>
<td>Remote ischemic preconditioning</td>
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<td></td>
<td>Cyclic limb ischemia with blood pressure cuff inflation</td>
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<td>Partial aortic balloon occlusion</td>
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<tr>
<td>Collateral flow augmentation</td>
<td>Increased oxygen delivery</td>
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<td>Nitric oxide donors such as pantoxiphylline</td>
<td>Normobaric oxygen; hyperbaric</td>
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<td></td>
<td>Perfluorocarbons</td>
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<td>Minimization of early cerebral edema</td>
<td>Decrease tissue oxygen consumption</td>
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<td>Glyburide</td>
<td>Therapeutic hypothermia</td>
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<td>Sensory stimulation</td>
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and pterygoplatine canal into the vicinity of the sphenoplatine ganglion. After an initial feasibility and safety study published as an abstract, IMPACT-24A (Implant Augmenting Cerebral Blood Flow Trial 24A) was initiated, aiming to show efficacy and safety of SPGS in nonlacunar anterior circulation stroke when initiated within 24 hours after stroke. The trial was halted after about half of the intended population was enrolled and the analysis of the trial showed no safety concerns and no overall benefit, the latter potentially due to underpowering.56 In the subsequent IMPACT-24B trial, the authors concluded that SPGS is safe 8–24 hours after ischemic stroke in patients who were ineligible for thrombolytic treatment.45 These findings suggest a research opportunity that early intervention may reduce the infarct growth velocity at the hyperacute stage of ELVO.

Transcranial brain electrical stimulation is another modality being exploited as a possible intervention for neuroprotection in acute stroke and a single-center study in which transcranial direct current stimulation is applied to the ischemic region in patients with ELVO undergoing EVT is ongoing (ClinicalTrials.gov NCT04061577).

**Neuroprotectants**

Pharmacologic approaches have also been suggested to reduce baseline tissue energy demands. In rodent models of ELVO, selective glutamate receptor antagonism reduces peri-infarct depolarizations and final infarct growth.50 One example is neriinetide, a neuroprotective agent that showed good results in preclinical studies with inhibition of postsynaptic density 95 and lowering of excitotoxicity following stroke. While primary outcomes were similar between neriinetide vs placebo arms in a study, the latter potentially due to alleleplase with disappearance of treatment effect in those who received aleplase. If offered early, these interventions hold promise in protecting penumbra and arresting the infarct growth prior to recanalization. Trials are underway to examine the role of ketamine for reducing infarct growth in humans. Other neuroprotective agents that have failed historically might warrant reconsideration in the age of reperfusion and faster treatment processing.

**Discussion**

A large degree of variability exists in infarct progression rate, with fast-progressors contributing to the greatest proportion of patients who do not achieve functional independence despite successful recanalization. The pathophysiologic determinants of the core infarct progression are wide and variable, mainly derived from the balance between brain energy consumption and collateral perfusion supply. Future research will be needed to better predict the infarct progression in individual patients with stroke and to implement appropriate theranostics strategies to minimize penumbral loss from field to the angiography suite.

**Study Funding**

No targeted funding reported.

**Disclosure**

H. Saber reports no disclosures. D.S. Liebeskind is consultant to Cererovus, Genentech, Medtronic, and Stryker. Go to Neurology.org/N for full disclosures.

**Publication History**

Received by Neurology June 28, 2020. Accepted in final form March 1, 2021.

**Appendix Authors**

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<tr>
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<td>UCLA</td>
<td>Study concept, drafting and revising the manuscript</td>
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