Collateral Circulation Augmentation and Neuroprotection as Adjuvant to Mechanical Thrombectomy in Acute Ischemic Stroke

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Abstract

Purpose of the Review
Mechanical thrombectomy (MT)–mediated endovascular recanalization has dramatically transformed treatment and outcomes after acute ischemic stroke caused by a large vessel occlusion (LVO). Current guidelines recommend MT up to 24 hours from stroke onset in carefully selected patients based on favorable clinical and imaging parameters. Despite optimal patient selection and low complication rates with current recanalization technology, approximately 1 in 2 patients with LVO stroke do not achieve functional independence at 3 months. This ceiling effect of MT efficacy may be explained by ischemic core expansion into the ischemic penumbra before recanalization and neuronal loss occurring after recanalization. Factors affecting the efficacy of MT, or the degree of irreversible injury, include time from symptom onset to recanalization, collateral circulation status, and differences in neuronal vulnerability. The purpose of this brief review is to discuss potential targets for neuroprotection, present and future potential pharmacologic and nonpharmacologic agents, and the data available in the literature.

Recent Findings
In experimental ischemia models, several authors reported that pharmacologic and nonpharmacologic agents are able to slow the progression of ischemic core expansion. However, in the era of unsuccessful recanalization of the occluded artery, several neuroprotective agents that were promising in the preclinical stage failed phase II/III clinical trials.

Summary
Providing neuroprotection before and after recanalization of an LVO may play an important role in improving outcomes in the era of MT. Neuroprotection is classically defined as a process that results in the salvage, recovery, or regeneration of neuronal (and other supporting CNS cell) structure or function. The advent of successful recanalization of acute LVO by MT in the majority of patients may spur the growth of effective neuroprotection.
Acute ischemic stroke (AIS) is a neurologic emergency characterized by severe disability and death. The economic impact of stroke from large vessel occlusion (LVO) is particularly high. Data from 2008 reveal that the total costs (direct and indirect) of treating LVO in the United States is approximately $34.3 billion and the total annual cost in the 27 EU countries is about €27 billion.²,³

Multiple randomized controlled trials (RCTs) (MR CLEAN, ESCAPE, EXTEND IA, SWIFT-PRIME, REVASCAT, DAWN, and DEFUSE) have demonstrated the superiority of mechanical thrombectomy (MT) over medical management for acute LVO stroke treatment.⁴⁻¹⁰ These trials showed that effective recanalization leads to reperfusion of ischemic brain tissue and can prevent further tissue injury or loss up to 24 hours after last seen well time. Effective recanalization is strongly associated with improved functional outcomes (4- to 5-fold).¹¹ However, despite high rates of complete recanalization in these trials, good outcome (defined as modified Rankin Scale [mRS] ≤2 at 90 days) was only achieved in 33%–71% of patients.⁴⁻ⁱ⁰ Time sensitivity of the cerebral tissue to ischemia has been extensively documented.¹²,¹³ Short time from symptom onset to recanalization, selection of patients with small ischemic core volume, and good collateral circulation improves the odds of good clinical outcome. Time to successful recanalization had an estimated 9% increased risk of death per 30-minute delay from symptom onset to recanalization.¹⁴⁻¹⁶ In another analysis, a 30-minute delay in recanalization increased the risk of moderate or severe disability by 7.0% and the risk of death by 11.8%.¹⁶

Emerging literature confirms clinical suspicion of the presence of large heterogeneity in neuronal tissue resistance to ischemia. High variability has been noted in the rate of neuronal loss and infarct growth in acute stroke secondary to LVO.¹⁷,¹⁸ The data suggest that powerful mechanisms to resist ischemia are in place and may be augmented by pharmacologic or nonpharmacologic agents. The current high rates of successful recanalization due to tremendous advancements in MT technology render it less likely that further improvement in devices will translate to a dramatic improvement in functional outcome: effective neuroprotection could break this ceiling effect. Neuroprotection is classically defined as a process that results in the salvage, recovery, or regeneration of neuronal (and other supporting CNS cell) structure or function.¹⁹ In this context, we refer to neuroprotection as the administration of pharmacologic and nonpharmacologic agents that slow the progression of ischemic core expansion—these have predominantly been investigated in the pre-MT era. However, at the time of unsuccessful recanalization of the occluded artery, several neuroprotective agents that were promising in the preclinical stage failed phase II/III clinical trials. To fully address the issue of neuroprotection in ischemic stroke, in 2019, the NIH as part of the Stroke Preclinical Assessment Network started to fund a nationwide preclinical trial platform. This remarkable endeavor is specifically designed to implement research aimed to test new treatments for AIS in experimental ischemia.

This review highlights key cellular targets and pharmacologic possibilities for neuroprotection, as well as nonpharmacologic approaches (Figure).

### Basic Science

The remarkable clinical outcomes achieved by rapid and effective endovascular recanalization suggest that the efficacy of neuroprotective agents may be optimal peri/postrecanalization (and conversely, less successful in its absence), as they may require a vascular route to reach the target tissue: the ischemic penumbra. The penumbra is a region of brain tissue where blood supply is limited, but it is potentially salvageable with reperfusion if neuroprotective agents are present to prevent cell death.²⁰,²² Much of in vivo basic science research in experimental ischemia has focused on slowing down core progression and protecting penumbral tissue.²³ Basic science research in experimental ischemia is beginning to reveal the complexity of several underlying pathophysiologic pathways in capillaries, glia, and neurons after occlusion of a major cerebral artery.²⁴,²⁹ Although many questions remain unanswered, several therapeutic targets for neuroprotection have been identified in both animal and early human studies that address excitotoxicity, energy substrates, antioxidants and oxygen delivery, blood flow/collateral stimulation, thrombolysis, neurostimulation, and anti-inflammatory pathways.²⁶ Specific targets have included NMDA receptors, GABA-B receptors, glutamate receptors, AMPA receptors, opioid receptors, sodium channels, potassium channels, calcium channels, leukocyte migration and adhesion factors, free radical scavengers, and apoptosis mediating factors.²⁶ Pharmacologic agents aimed at these targets have reduced final infarct volume by 30%–50% and improved neurologic outcomes in early human studies.²⁵⁻²⁷,²⁹ However,
although several of these neuroprotective agents were initially promising in acute stroke, they failed phase II/III clinical trials. Here, we highlight pharmacologic targets for excitotoxicity, apoptosis, blood flow/collateral stimulation, and increasing oxygen delivery.

**Excitotoxicity**

A significant body of preclinical research has focused on salvageable ischemia at a cellular level, and particularly on the concept of “excitotoxicity” and the downstream effect of excessive activation of glutamate receptors. After occlusion of the middle cerebral artery, ATP depletion leads to failure of ion pumps maintaining membrane polarization. Subsequent depolarization caused by initial rise in cytoplasmic Ca\(^{2+}\) and Na\(^+\) from ion pump failure, in addition to increased Ca\(^{2+}\) and Na\(^+\) influx due to NMDA and AMPA receptor activation by glutamate, ultimately leads to persistently increased cytoplasmic Ca\(^{2+}\) levels—the effects of this are nuanced and multidimensional, but predominantly cytotoxic.

**Nerinetide (Na1)**

It is well established that overactivation of the NMDA receptors (NMDARs) and the resulting calcium influx promotes cell death, rendering this receptor a key mediator of excitotoxicity. NMDARs are heterotetramers typically composed of 3 major subunit types, including a GluN1, 2 regulatory GluN2 subunits, and less commonly GluN3 units. The interaction between postsynaptic density protein 95 (PSD95) and GluN2B as a cause and potential therapeutic target in stroke-mediated excitotoxicity led to the development of Tat-NR2B9c, a peptide that disrupts this interaction. After data on efficacy in vitro, in vivo, and in a primate model of stroke, Tat-NR2B9c (Na1) has been tested in RCTs. ENACT, a phase II trial, tested the safety and efficacy of Na-1 in patients with iatrogenic stroke after endovascular aneurysm repair and reported fewer ischemic infarcts vs placebo. The more recently published ESCAPE-NA-1 is a multicenter double-blind, placebo-controlled, RCT in patients with acute LVO undergoing MT designed to determine the safety and efficacy of IV nerinetide (Na-1). The participants were randomized to undergo IV infusion of nerinetide or placebo before recanalization of the occluded artery by MT. The study included 1,105 treated by MT (with or without alteplase) within 12 hours of symptom onset. Patients were randomly assigned (1:1) to receive IV nerinetide (2.6 mg/kg, n = 549) or placebo (saline, n = 556). Similar 90-day clinical outcomes were noted between the 2 groups: 337/549 nerinetide (61.4%) and 329/556 placebo (59.2%) obtained an mRS score of 0–2 (adjusted risk ratio 1.04, 95% confidence interval [CI] 0.96–1.14; \(p = 0.35\)). Secondary outcomes and serious adverse events were similar between the 2 groups. However, within the cohort that did not receive alteplase, more patients treated with nerinetide vs placebo achieved favorable outcome (59.3% vs 49.8%, relative risk 1.18, CI 1.01–1.38). This is attributed to a potential drug–drug interaction as peak plasma nerinetide concentrations were noted in patients who were also treated with alteplase. Whereas the overall tradeoff between MT + nerinetide vs MT – alteplase has not been explored, the findings of nerinetide benefit in the nonalteplase
subcohort support the possibility of neuroprotection and warrant further exploration.

**Magnesium Sulfate**

Magnesium sulfate, inexpensive and easily administered in the pre- and intrahospital setting, has been shown to decrease the rates of cerebral palsy among preterm babies, and is also routinely used as a prophylactic agent for seizures in preeclamptic women. Animal models were encouraging and demonstrated significant reduction in infarct size after induction of focal brain ischemia. The mechanism of neuroprotection is thought to be multifactorial, including vasodilatory effects and direct biological neuroprotective and glioprotective effects from NMDAR blockade and anti-inflammatory effects. Given its potential as a neuroprotectant, it has been studied in 7 RCTs for AIS. The most recent, the FAST-MAG trial, enrolled 1700 patients and randomized them into magnesium vs placebo groups. There was no significant shift in the distribution of 3-month mRS scale score ($p = 0.28$) or proportion of mortality ($p = 0.95$) between the 2 groups. Similarly, a meta-analysis of 7 trials did not observe any improvements in outcome after magnesium administration. However, none of these trials exclusively evaluated magnesium sulfate combined with successful MT, and further studies in selective cohorts may be informative.

**Apoptosis**

Research on slowing down ischemic core progression while simultaneously protecting the penumbra has explored causes of early cell death mostly via glutamate-induced intracellular Ca$^{2+}$ elevation. After the initial insult, delayed cell death may occur via apoptotic mechanisms, such as those triggered by the mitochondrial release of cytochrome C.

Nitric oxide (NO), implicated in downstream neurotoxic cascades, is synthesized by neuronal NO synthase, which is dependent on binding of the Ca$^{2+}$-sensitive enzyme calmodulin. NO reacts with superoxide anions to form a ONOO-, a highly reactive oxidant that promotes tissue damage. This is just one example of the role played by reactive oxygen species (ROS) and reactive nitrogen species in cell damage following the activation of enzymes like calpains, proteases, NO synthase, and calcium.

The damage caused by the production of ROS includes abnormal changes in the organization of the cytoskeleton, mitochondrial dysfunction, the formation of inflammatory molecules, and the triggering of signaling pathways resulting in apoptosis. Neuroprotection in the form of free radical scavengers has thus been proposed in experimental models of focal ischemia. Scavengers of NO including PTIO (2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide) and pyrroliodinated hemoglobin polyoxyethylene conjugate (PHP) have shown promise in the treatment of NO-mediated disease states in preclinical models. Beyond free radical generating effects of NO, it is also involved in cerebral blood flow regulation due to its vasodilatory effects rendering ubiquitous inhibition potentially problematic. Mice data suggest that maintaining NOS activity is essential to penumbral perfusion via collateral blood flow. Other ROS scavengers including edaravone have been approved in Japan for ischemic stroke treatment. NXY-059, a free radical scavenger, has been tested in the SAINT trial for AIS, but had disappointing results.

**Activated Protein C**

Neuroprotective effects of activated protein C (APC) are wide-ranging, from anti-inflammatory to anti-apoptotic. There is an inverse relationship between APC and incidence of stroke. APC elevation has been noted during carotid endarterectomy and decreased levels of APC are found in stroke patients with infection (vs those without). Combined, this suggests that APC may have neuroprotective properties or be an epiphenomenon marker of disease. Murine models of focal ischemia suggest that human APC can reduce infarct size by reducing p53 in cerebral microvasculature, reducing apoptosis and promoting vascular integrity. A recombinant variant of human APC was studied in combination with acute reperfusion therapy for AIS in the RHAPSODY trial. The primary end point of this trial was vasculoprotection, adjudicated as intracranial hemorrhage posttreatment. A total of 110 patients were enrolled and a trend towards lower hemorrhage rate was observed without any significant effect on efficacy outcomes. Future studies with robust study designs and larger sample sizes are warranted.

**Collateral Circulation as Target for Neuroprotection**

Another possible strategy for neuroprotection in AIS is augmentation of collateral circulation. In experimental ischemia, middle cerebral artery occlusion (MCAO) induces redistribution of cerebral blood flow (CBF) and engagement of the leptomeningeal collateral vessels. The degree of CBF redistribution is demonstrated by the size and number of pial collaterals in both experimental ischemia models and patients with LVOs. Blood flow augmentation in leptomeningeal anastomosis (LMA) can significantly influence outcomes. Increased pial collateral flow during MCAO reduces heat shock protein induction and reduces protein synthesis inhibition, associated with penumbral tissue, providing protection from the progression of the ischemic. Conversely, poor flow in the pial collaterals is associated with faster ischemic core progression and larger final infarct volume. Status of the collateral circulation also has implications for patient stratification and selection for MT in acute LVOs. Several authors have reported the strong correlation between robust collateral circulation and favorable outcomes following successful recanalization of LVOs.

Another important piece of evidence in LMA physiology is that in acute ischemia even the most robust collateral circulation does not last forever. In normotensive rats, redistribution of blood flow in the distal middle cerebral artery (MCA)/anterior cerebral artery borderzone region occurring immediately after MCA occlusion (MCAO) has been shown to gradually subside over a 2-hour period. In contrast, in both
spontaneously hypertensive rats and rats with renal hypertension, the ischemic penumbra was present after just 30 minutes of occlusion and decreased dramatically at 90 minutes with a rapid expansion of the ischemic core and minimal or no penumbra. Chronic arterial hypertension thus reduced sustainability of collaterals and may be an important consideration in developing collateral-enhancing targets. e9,e10

**Potential Targets for Collateral Enhancement**

Investigators have hypothesized that the loss or lack of dilation of leptomeningeal arterioles during MCAO is an important target that could improve outcome after acute stroke. For example, endothelin A receptor antagonists may prevent the collapse of penumbral flow and improve reperfusion.e11-e13 Another strategy for opening vasoconstricted pial arteriolar collateral vessels is rho-associated protein kinase (ROCK) inhibition. ROCK is expressed and activated in numerous cell types including vascular smooth muscle, endothelium, neurons, glia, and immune cells.e14-e16 Abnormal activation of ROCK is thought to have a key role in numerous pathologies, including hypertension, diabetes, and atherosclerosis, all cerebrovascular risk factors known to be associated with unfavorable outcome after stroke. ROCK activation has also been connected with injury in ischemic stroke via hemodynamic and microvascular dysfunction, inflammation, and oxidative stress.e17-e21 Preclinical work has also demonstrated that ROCK inhibition in both normal and diseased animals improves outcome after ischemic stroke through several mechanisms including collateral flow augmentation.e17-e22 ROCK has been shown to be involved in myogenic vasoconstriction, making it a potentially important and unique target to open collateral vessels. e20,e22,e23

Other potential targets for collateral augmentation and opening include NO donors. These are being evaluated in clinical trials to possibly extend the therapeutic window for endovascular thrombectomy and tissue plasminogen activator. Hyperconstricted LMAs from spontaneously hypertensive rats were unresponsive to dilation by the NO donor sodium nitroprusside.e24 Normotensive and aged rats responded to sodium nitroprusside and were able to dilate 60%–80% of maximum, but LMAs from hypertensive rats had markedly reduced response, and dilated only ~20%,e24 If this is also true in humans, a potentially large subpopulation of patients with stroke will not respond to NO donor strategies and this approach may be limited. NO has been implicated as a proinflammatory mediator and may further limit its neuroprotective potential. This is an example highlighting the complexity of stroke treatment and the importance of the state of the premorbid vasculature.

**Oxygen Delivery**

Hemoglobin-based oxygen carriers (HBOCs) as transfusion media have been investigated for decades. One of the first-generation HBOCs was a cross-linked hemoglobin (Hb) tetramer with a P50 of 32 Torr. This was tested in clinical trials of hemorrhagic shock and ischemic stroke. These trials failed likely due to peripheral effects and scavenging NO that caused vasoconstriction, and loss of oxygen in precapillary arteries and arterioles. In addition, time to treatment was as long as 18 hours, which we know now is likely too late for many patients with stroke. Subsequently cell-free HBOCs were developed as large polymers to prevent extravasation into tissues (e25,e28 e.g., Hb Polytaur with P50 = 17 Torr and zero-linked bovine HBOC with P50 = 4 mm Hg). These were found to reduce infarct size in mice with transient MCAO when exchange transfusions were performed with large fluid volumes.e29

**PP-007 (PEGylated carboxyhemoglobin)**

Recently, a polyethylene glycol–modified HBOC in the carboxy state (PEG-COHb) to prevent auto-oxidation to metHb and extend shelf life was used in a top-loaded fashion (i.e., injection, not transfusion) and was found to be efficacious in a rat model of MCAO.e25-e30 The IV treatment volume of the solution containing 4 g/dL Hb was 10 mL/kg, which was much less than that used with polymer Hb. The mechanism of improved stroke outcome in preclinical models was thought to be due to a combination of oxygen transport, dilation of pial collaterals that salvaged the penumbra by release of CO, and anti-inflammatory effects of low amounts of CO (COHb <2%).e25 Evidence for improved oxygenation was supported by less conversion of pimonidazole to protein adducts (known to occur in severely hypoxic tissue) and by decreased expression of HIF-1α in the MCA territory. PEG-COHb, PP-007, has an increased molecular radius, which prevents extravasation through the endothelium.e31 Thus, this generation of HBOC can vasodilate pial arteriolar and improve oxygenation in ischemic tissues. Furthermore, when infused at reperfusion in mice, it was found to reduce proinflammatory cytokine expression. This effect was attributed to its acting as a CO donor (small amounts of CO are anti-inflammatory).e32

Recently, PP-007, a pegylated carboxyhemoglobin oxygen carrier, was shown to significantly increase cerebral blood flow in LMA after MCAO in spontaneously hypertensive rats (SHRs).e33 The acute brain injury volume was also significantly decreased in PP-007–treated rats during early treatment vs vehicle-treated rats (28.8 ± 3.2% vs 18.8 ± 2.3%; p < 0.05). The PP-007 ability to increase collateral flow in SHRs suggests that it may improve acute stroke-related outcomes as an adjunct to endovascular therapy.

Interestingly, PP-007 may deliver more oxygen than Hb contained in red blood cells (RBCs) because of increased diffusional surface area in plasma and by facilitation of oxygen transport from RBC to endothelium. This is due to the p50 of 12, which is in between that of RBCs vs hypoxic tissue. It may also reduce RBC size and endothelial/astrocyte swelling because of its hyperoncotic effect. PP-007 does not extravasate into tissue and limits precapillary oxygen loss.e34,e35 Another mechanism underlying PP-007 neuroprotection is dilation of pial arterioles (LMA), which can salvage penumbra in those patients who have a small ischemic core. Moreover, plasma expansion effects of PP-007 increase LMA blood flow by increasing blood volume. Dilation of collaterals and other vessels by diffusion of CO may improve the effectiveness of reperfusion after successful recanalization.
The safety of PP-007 in AIS patients with LVO who are candidates for MT will be investigated in a phase 1 clinical trial. In HEMERA-1 (Safety Study of PP-007 in Subjects With Acute Ischemic Stroke), acute stroke patients with LVO will be randomized 4:1 to placebo. Collateral circulation status and final infarct volume will also be assessed as secondary outcomes.

Nonpharmacologic Neuroprotection

Nonpharmacologic neuroprotection to slow down core expansion and preserve penumbral tissue may complement pharmacologic measures and can be minimally invasive and easy to administer.

Normobaric Hyperoxia

Normobaric hyperoxia (NBO) is a well-studied nonpharmacologic approach to decelerate core expansion and preserve penumbra. Extensive work in both published phase II RCTs of NBO documented feasibility and safety but found no clinical benefit.\(^ {36,37} \)

Sphenopalatine Ganglion Stimulation

Sphenopalatine ganglion stimulation (SPG) to augment cerebral blood flow was recently tested in a randomized, sham-controlled, double-blinded trial in 303 patients with anterior circulation ischemic stroke who were not treated with reperfusion therapies within 24 hours. Patients were randomly allocated to active SPG stimulation or sham control. A sliding dichotomy of the 90-day mRS was used as the primary efficacy outcome, with a modified intention-to-treat population. The trial, initially planned for 660 patients, was terminated early due to technical improvements in device placement. In the 303 patients analyzed, SPG stimulation did not improve 3-month disability. However, the authors noted a significant treatment interaction with cortical vs noncortical stroke location (\( p = 0.04 \)). In those with cortical involvement (\( n = 87 \)), rates of improvement were 50.0% vs 27.0% (odds ratio 2.70, 95% CI 1.08–6.73; \( p = 0.03 \)). There was no difference in mortality, safety, or serious adverse events.\(^ {38} \)

Hypothermia

Lastly, several preclinical and clinical studies have explored the utility of hypothermia to provide neuroprotection in the setting of an AIS.\(^ {39} \) Therapeutic hypothermia in the acute phase of stroke may reduce cerebral metabolism,\(^ {40} \) improve brain glucose utilization,\(^ {41} \) and has the potential to halt the entire ischemic cascade.\(^ {42} \) This may lead to improved cerebral autoregulation and decrease consequent hyperemia following reperfusion.\(^ {43} \) There have been many trials studying therapeutic hypothermia and systemic and endovascular cooling.\(^ {44–48} \) One of the largest prospective nonrandomized cohort studies was performed in 113 patients and reported intraarterial selective cooling infusion in patients treated with MT was safe and the authors observed a trend towards improved outcomes compared to the control arm patients (mRS 0–2.51% vs 41%, odds ratio 1.9, CI 0.8–2.6; \( p = 0.192 \)).\(^ {49} \) Ongoing technical advances may realize the therapeutic potential of targeted hypothermia in acute stroke. This strategy may need to be implemented differently in patients with vs without LVOs.

Summary

MT has proven to be a powerful treatment for AIS in the setting of LVO. Nevertheless, time from symptom onset to recanalization, high variability in collateral circulation status, and ischemic core expansion may limit the extent and number of patients who may benefit from successful recanalization. Tremendous recent advancements in MT technology suggest that further device improvement may have diminishing returns in terms of effect on disability after acute LVO. Combining neuroprotection with MT provides an unprecedented opportunity for a new wave of discovery and improvement in LVO outcomes. Understanding basic neurovascular pathophysiologic mechanisms of core expansion, collateral preservation, and resilience to ischemia will help us identify potential high-yield targets to improve outcomes for patients with this devastating disease.

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Appendix  Authors

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