Reperfusion Therapies for Acute Ischemic Stroke
Current Pharmacological and Mechanical Approaches
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Background and Purpose—Arterial recanalization and subsequent reperfusion have extensively demonstrated their ability to restore the brain function when performed shortly after acute ischemic stroke. However, arterial recanalization does not necessarily lead to brain tissue reperfusion.

Summary of Report—This review provides an update of current approaches to improve the efficacy profile of brain tissue reperfusion within and beyond the therapeutic window, including the use of novel thrombolytic agents, bridging intravenous and intra-arterial therapies, and mechanical clot retrieval or aspiration.

Conclusions—There are still several challenges in the near future of reperfusion therapy for acute ischemic stroke, such as improving the ultra-early access to treatment within the “golden hour,” extending the therapeutic window beyond the current 4.5-hour time window, and developing novel thrombolitics or combined approaches to improve treatment efficacy.

Improving the Ultraearly Access to Treatment Within the ‘Golden Hour’
Several strategies are under development for increasing the access to treatment by shifting more eligible patients to the first 60 minutes of stroke onset when the treatment has shown to be much more effective. Tele-thrombolysis is an easy and feasible approach that is being increasingly implemented for rapid evaluation and treatment of patients in the community hospital, avoiding unnecessary transfers and delays in treatment initiation. The feasibility and cost-effectiveness of ambulances implemented with portable CT scans and transcranial Duplex ultrasound are currently under evaluation.

Widening the Therapeutic Window for Intravenous Tissue Plasminogen Activator Beyond 4.5 Hours
Several studies and meta-analyses have shown that in unsolicited patients with ischemic stroke, intravenous tissue plasminogen activator (tPA) may be moderately beneficial when given beyond 3 hours. The European Cooperative Acute Stroke Study (ECASS) III trial, a double-blind, placebo-controlled study of intravenous tPA, has demonstrated that intravenous tPA given between 3 and 4.5 hours of stroke onset was significantly associated with a good clinical outcome (modified Rankin Scale score 0 to 1) compared with placebo with an acceptably low rate of symptomatic intracranial hemorrhage. An updated pooled analyses, including ECASS, National Institute of Neurological Disorders and Stroke (NINDS), Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), and
Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) trials, showed that for CT-based thrombolysis <4.5 hours, the odds of a favorable 3-month outcome increased as time to treatment decreased and no benefit of intravenous tPA was seen after approximately 270 minutes. Beyond 4.5 hours, risk might outweigh benefit.

Nevertheless, the majority of patients with stroke arrive to emergency departments late, and it is necessary to improve the selection of patients beyond the 4.5-hour time window. The potential clinical gains from tPA relate to tissue reperfusion and attenuation of infarct growth, which depend on the degree of irreversible damage and the presence and extent of the ischemic penumbra. The penumbra can be evaluated with echoplanar MRI, diffusion-weighted MRI, and perfusion-weighted MRI. Diffusion-weighted imaging lesions are regions of cytotoxic edema, which usually proceed to infarction, and the mismatch between a larger perfusion-weighted imaging lesion and smaller diffusion-weighted imaging lesion is thought to be a signature of the ischemic penumbra. The probability of infarction depends on the severity and duration of hypoperfusion in the ischemic penumbra. Therefore, imaging of the penumbra might allow selection of patients for thrombolysis beyond 4.5 hours.

The Diffusion Weighted Imaging Evaluation for Understanding Stroke Evolution study (DEFUSE) was a prospective nonrandomized pilot study of intravenous tPA in patients with hemispheric stroke between 3 and 6 hours of symptom onset. The aim of DEFUSE was to identify patient subgroups that are likely to have a favorable response to intravenous tPA administered between 3 and 6 hours after stroke onset based on pretreatment MRI profiles. DEFUSE identified 4 discrete MRI patterns that appear to predict differing clinical responses to early reperfusion after tPA therapy. DEFUSE also demonstrated that patients with middle cerebral artery or internal carotid artery occlusion have relatively low rates of complete (22%) or partial (22%) early recanalization after intravenous tPA therapy. EPITHET was a multicenter randomized placebo-controlled trial aimed to test whether tPA given 3 to 6 hours after stroke onset promotes reperfusion and attenuates infarct growth in patients who have a mismatch in perfusion-weighted imaging and diffusion-weighted imaging. A total of 101 patients were included in this study; 52 patients were randomly assigned to intravenous tPA and 49 patients to placebo. Eighty-five of 99 (86%) patients had a mismatch in perfusion-weighted imaging and diffusion-weighted imaging. The geometric mean infarct growth (exponential of the mean log of relative growth) was 1.24 with tPA and 1.78 with placebo (ratio 0.69; 95% CI, 0.38 to 1.28; \( P = 0.239 \)); the median relative infarct growth was 1.18 with tPA and 1.79 with placebo (ratio, 0.66; 0.36 to 0.92; \( P = 0.054 \)). Reperfusion was more common with tPA than with placebo and was associated with less infarct growth (\( P = 0.001 \)), better neurological outcome (\( P < 0.0001 \)), and better functional outcome (\( P = 0.010 \)) than no reperfusion.

**Improving the Efficacy of Thrombolysis Within the 4.5-Hour Window**

The failure of tPA to achieve rapid reperfusion in many patients and its bleeding risk have prompted the development of fibrinolytic agents with greater fibrin specificity and better risk–benefit profiles. Novel agents that achieve higher recanalization rates, lower hemorrhage rates, or both would extend the time window in which intravenous fibrinolytic therapy is beneficial. Tenecteplase (TNK) is a genetically modified form of tPA that has 14-fold greater fibrin specificity, a longer half-life, and 80-fold greater resistance to inhibition by plasminogen activator inhibitor type 1. The long lifetime of TNK allows the use of a single bolus. High fibrin specificity should confer the ability to induce faster and more complete clot lysis with less bleeding complications. In a pilot dose-escalating study, 75 patients with stroke were treated with intravenous TNK <3 hours after symptom onset. Patients were enrolled in 3 dose tiers of TNK: 0.1, 0.2, and 0.4 mg/kg. No case of symptomatic intracerebral hemorrhage was observed during the first 72 hours after treatment. TNK for the treatment of acute ischemic stroke has been recently investigated in a Phase IIb/III trial. The trial was prematurely stopped due to the low recruitment rate and no differences were found between 3 doses of TNK (0.1, 0.3, and 0.4 mg/kg) and the standard dose of tPA. Recently, our group studied 122 consecutive patients with stroke due to middle cerebral artery occlusion who fulfilled criteria for intravenous thrombolysis. Patients were allocated to receive 0.9 mg/kg standard intravenous tPA (10% bolus, 90% 1-hour infusion) or 0.4 mg/kg intravenous TNK (bolus). After 2 hours of treatment, recanalization was significantly \(( P = 0.028)\) higher in the TNK group \((n=29 [69%])\) as compared with the tPA \((n=43 [53%])\) group. Complete recanalization at 2 hours was seen in 18 (42.4%) and 27 (33.4%) patients treated with TNK and tPA, respectively \(( P = 0.014)\). Symptomatic intracerebral hemorrhage occurred in 1 (2.3%) and 3 (3.7%) TNK and tPA patients, respectively. At 24 hours, 63% and 51% of TNK and tPA, respectively, improved by >4 points in the National Institutes of Health Stroke Scale score. TNK increased 2.5-fold the rate of dramatic clinical recovery at 24 hours as compared with tPA \((24.5\% \text{ versus } 11\%)\). Parsons et al reported the results of a prospective pilot study of 15 patients selected by CT or MRI diffusion/perfusion mismatch and treated with intravenous TNK at a dose of 0.1 mg/kg between 3 and 6 hours from stroke onset. Compared with a nonrandomized control group of 35 patients treated with standard recombinant tPA within the 3-hour time window, more TNK-treated patients had major neurological improvement at 24 hours (66.7% versus 20.0%) as well as improved reperfusion and large vessel recanalization compared with the tPA-treated group. These observations suggest that further study of TNK as an alternative treatment for acute ischemic stroke may be warranted.

Desmoteplase is 1 of 4 distinct proteases found in the saliva of the blood-feeding vampire bat *Desmodus rotundus*, collectively referred to as *D. rotundus* salivary plasminogen activators. Desmoteplase induces faster and more sustained recanalization than tPA and produces less antiplasmin consumption and fibrinogenolysis. Desmoteplase has shown promise in 2 Phase II ischemic stroke trials enrolling patients 3 to 9 hours after onset when an MRI diffusion–perfusion mismatch pattern is present. However, DIAS II, a Phase III trial of *D. rotundus* salivary plasminogen activator, showed...
that the proportion of patients who achieved good outcome at 3 months was comparable in patients who received 90 mg/kg and placebo (45%) and surprisingly lower in those treated with the highest dose of D. rotundus salivary plasminogen activator (35%). The unexpected good response of the placebo groups may suggest imbalance among treatment arms. Currently, the Desmoteplase in Acute Ischemic Stroke Trial (DIAS) III/IV trial is enrolling patients to either D. rotundus salivary plasminogen activator or placebo in the 3- to 9-hour window using vessel occlusion instead of the presence and extent of mismatch for patient selection.

Combination pharmacotherapy strategies to expand the intravenous fibrinolysis time window beyond 4.5 hours are under active investigation. A rational combination of agents with additive effects on clot lysis and clot formation may yield higher rates of arterial recanalization, lower rates of reocclusion, reductions in the dose of fibrinolytic agent required, and reduced frequency of hemorrhage transformation. Coadministering agents that block blood–brain barrier degradation may markedly reduce hemorrhagic complications of fibrinolysis, permitting extension of therapy to a wider range of patients. Combination therapy with fibrinolytic and GP IIb/IIIa agents is under wide-ranging investigation.

Experimental and clinical studies have consistently demonstrated the capability of ultrasound to enhance enzymatic thrombolysis. Ultrasound application increases the transport of tPA into the thrombus, promotes the opening and cleaving of the fibrin polymers, and improves the binding affinity of tPA to fibrin. Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST), a Phase 2 multicenter randomized trial, recently demonstrated that 2-hour continuous monitoring with 2-MHz transcranial Doppler, a commercially available device widely used for diagnosis, in combination with standard tPA is safe and may improve outcome. Among 126 patients randomized to tPA plus 2-hour transcranial Doppler monitoring (target group) or tPA alone (control group), symptomatic intracerebral hemorrhage occurred in 4.8% of target and 4.8% of control patients. Complete recanalization or dramatic clinical recovery at 2 hours after tPA bolus was observed in 49% of target and 29% of control patients (P=0.02). Moreover, trends toward better clinical outcomes at 24 hours and long term were noted in sonothrombolysis patients. Enhancement of enzymatic thrombolysis by ultrasound may allow testing regimens with low-dose tPA to reduce the risk of intracerebral hemorrhage. The capability of microbubbles to further accelerate ultrasound-enhanced lysis in patients with stroke is currently under investigation.

**Rescue Reperfusion Strategies**

Intra-arterial (IA) fibrinolysis has the potential to deliver the thrombolytic agent inside and round the clot using a reduced dose of thrombolytic. Moreover, mechanical clot disruption can be done facilitating clot lysis. However, this approach also has a number of potential disadvantages, including manipulation of a catheter within cerebral vessels, potentially increasing vulnerability to hemorrhage; the requirement for heparin administration intraprocedurally to prevent catheter-induced thrombosis (potentially increasing hemorrhage risk); delay in treatment initiation at the time the diagnostic angiogram is performed and the delivery microcatheter positioned; and the intervention limited only at tertiary hospitals capable of providing acute endovascular therapy.

A treatment strategy of combined intravenous/IA lytic therapy may combine the advantages of faster initiation of intravenous thrombolysis followed by rescue IA revascularization. In the Management of Stroke (IMS) trial, patients were treated with reduced-dose intravenous tPA (0.6 mg/kg over 30 minutes) initiated within 3 hours of onset followed by IA tPA, beginning within 5 hours of onset, if residual clot was visualized. Compared with historical controls treated with conventional intravenous tPA, patients treated with combined intravenous/IA tPA showed only a modest trend to improved clinical outcomes (OR for global test, 1.35; CI, 0.78 to 2.37). The IMS II implemented in the aforementioned protocol the administration of ultrasound by means of intravascular EKOS during IA drug delivery. The application of EKOS during IA was associated with a high rate of complete recanalization (69%) as compared with conventional combined intravenous plus IA revascularization approach (53%).

Mechanical recanalization has several advantages over pharmacological thrombolysis and may be used as primary or adjunctive strategies. It may reduce or preclude the use of lytic drugs and reducing the risk of intracerebral hemorrhage. If no thrombolytic drug is used, the time window for treatment could be extended beyond the limit of 6 to 8 hours. Moreover, mechanically thrombus fragmentation may increase the area of clot surface to be exposed to lytic agents accelerating thrombolysis. On the other hand, mechanical recanalization may be a reasonable therapeutic option for patients who have either a contraindication to pharmacological thrombolysis such as recent surgery or abnormal hemostasis or are late in their presentation.

Several mechanical techniques are currently available for removing clots from the intracranial arteries, including endovascular thrombectomy (Merci retriever device, Neuronet device, Catch device, Phenox clot retriever), endovascular thromboaspiration (Angiojet and Penumbra systems), temporary endovascular bypass (Solitaire), and augmentation of fibrinolysis (MicrolysisUS infusion catheter EKOS). Most of these systems have been tested in pilot multicenter noncontrolled studies showing high rate of recanalization (51% to 82%), which contrasts with the low rate of favorable outcome achieved (25% to 41%). The high rate of futile recanalization may be explained by factors unrelated to the technical success. Factors such as stroke severity, older age, systolic hypertension, extent of hypodensity, or brain swelling on pretreatment CT, and admission hyperglycemia, have been shown to be predictors of poor outcome in stroke thrombolysis. The beneficial effect of early restoration of cerebral blood flow on stroke outcome may be hampered in part by such factors as extent of irreversible brain injury before recanalization, excessive glucose burden at the time of reperfusion, and blood pressure changes during procedure. These factors are particularly crucial in the extended time window when the likelihood of success decreases over time. The use of general anesthesia during endovascular procedures has been recently demonstrated in a multicenter retrospective
study to be an independent predictor of poor clinical outcome. On the other hand, clinical trials of revascularization have been designed to achieve technical success and focused on recanalization as a primary efficacy end point. Prestroke disability (modified Rankin Scale score >1) may hamper the effect of treatment on stroke outcome independent of the occurrence of futile recanalization. Moreover, patients’ imaging selection should be improved. Preprocedural imaging (CT perfusion or diffusion-weighted MRI) may depict those patients with large, already infarcted tissue and improve the selection of patients for delayed revascularization. Future studies should be focused on identifying the optimal timing and best modality for preprocedural imaging evaluation. In essence, more careful patient selection to avoid futile recanalization is needed. Factors such as age, extent of irreversible ischemia, occlusion location, stroke severity, blood pressure, pattern of collateral flow, and pretreatment with tPA become critical in the late time window (>4.5 hours) and may play a central role in translating angiographic recanalization into a favorable clinical outcome. The development of multimodal outcome scores including these factors may help to improve the selection of patient for mechanical revascularization.

Disclosures
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References


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