Extending Reperfusion Therapy for Acute Ischemic Stroke
Emerging Pharmacological, Mechanical, and Imaging Strategies
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Background and Purpose—Reperfusion is the most beneficial of all therapeutic strategies for acute ischemic stroke. However, the standard cerebral reperfusion treatment of the first decade of the reperfusion era, noncontrast computed tomography (CT)–guided, ≤3 hours, intravenous tissue plasminogen activator, has many limitations. This review surveys emerging strategies that have the potential to extend cerebral reperfusion therapy to larger numbers of patients.

Summary of Review—Innovative intravenous pharmacological reperfusion strategies include novel fibrinolytic agents (tenecteplase, reteplase, desmetolplase, plasmin, and microplasmin), glycoprotein (GP) IIb/IIIa antagonists with platelet disaggregating effects (abciximab and tirofiban), combination therapies to improve efficacy of clot lysis (fibrinolytics and GP IIb/IIIa agents, and fibrinolytics and direct thrombin inhibitors), increase the time window for clot lysis (fibrinolytics and neuroprotectants), and reduce the frequency of hemorrhagic complications (fibrinolytics and vasoprotectants), and externally applied ultrasound to enhance enzymatic fibrinolysis. Promising intra-arterial pharmacological reperfusion approaches include novel fibrinolytic agents, combined intravenous and intra-arterial fibrinolysis, and combined fibrinolytics and GP IIb/IIIa agents. Emerging endovascular mechanical reperfusion strategies include intra-arterial thrombectomy (clot retrieval devices and suction thrombectomy devices), mechanical disruption (micro-guidewire passage, laser photoacoustic emulsification, and primary intracranial angioplasty), and augmented fibrinolysis by endovascular ultrasound. Multimodal imaging, with magnetic resonance (MR) or CT, can rapidly assess infarct core, penumbra, site of vessel occlusion, and tissue hemorrhagic propensity, enabling improved selection of patients for reperfusion therapy beyond any arbitrary fixed time window.

Conclusions—Therapeutic reperfusion is emerging as a treatment strategy of remarkable power and scope for rescuing patients experiencing acute brain ischemia, applicable within and beyond the 3-hour time window. (Stroke. 2005;36:2311-2320.)

Key Words: endovascular therapy ■ reperfusion ■ stroke, acute ■ thrombolysis

Reperfusion of the ischemic brain is the most effective therapy for acute ischemic stroke ever known and ever likely to be discovered. By restoring nutritional blood flow to threatened tissues before they progress to infarction, reperfusion therapies salvage penumbral tissue, reduce final infarct size, and enable improved clinical outcomes. In the decade since the advent of reperfusion as a proven treatment strategy in acute ischemic stroke, accumulated research data and clinical experience have confirmed the dramatic benefit of early cerebral reperfusion.1 Intravenous fibrinolytic therapy within 3 hours of onset yields a benefit at least an order of magnitude greater than aspirin, the only other widely available pharmacological agent of proven efficacy for ischemic stroke. Among patients matching the population in the pivotal National Institute of Neurological Disorders and Stroke (NINDS) trials, the number needed to treat for benefit is ≈3.1,2 For every 1000 patients treated, ≈323 will attain a better outcome. A worldwide consensus recognizing the efficacy of reperfusion therapy for stroke now exists, with within–3-hour intravenous tissue plasminogen activator (tPA) approved by independent drug regulatory authorities in the United States, Canada, South America, Australia, and the European Union.

However, the standard reperfusion strategy of the first decade of the reperfusion era, noncontrast computed tomography (CT)–guided, <3 hours, intravenous tPA, has many limitations, including a short treatment time window, achieved recanalization rates of only ≈50%, and a substantial risk of symptomatic hemorrhagic transformation. As a result,
few (typically 1% to 3%) patients currently receive reperfusion therapies in actual practice.

Several emerging strategies have the potential to extend cerebral reperfusion therapy to larger numbers of patients, including patients presenting beyond the current 3-hour time window. This review highlights recent advances shaping the coming era of expanded reperfusion treatments for acute ischemic stroke.

**Extending the Time Window for Conventional Intravenous tPA**

Pooled individual patient data analysis indicates that intravenous tPA may be of modest benefit beyond 3 hours in relatively unselected ischemic stroke patients. The ongoing ECASS-3 trial will confirm or disconfirm this finding in the 3- to 4-hour time window by enrolling 800 patients in a fully double-blind, placebo-controlled study. The International Stroke Trial 3 (IST 3) will also provide some data of interest, although lack of blinding and selection criteria that will allow enrollment of patients at hospitals that have not clearly made an institutional commitment to the safe delivery of thrombolytic therapy will make study interpretation difficult.

**Novel Fibrinolytic Agents**

The failure of tPA to achieve rapid reperfusion in many patients and its bleeding risk have prompted the development of more 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, 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 administration. High fibrin specificity should confer the ability to induce faster and more complete clot lysis, with less bleeding complications. TNK administration has been demonstrated to avoid the systemic plasminogen activation and plasmin generation commonly seen after tPA therapy. Further, the lack of a procoagulant effect exhibited by TNK may reduce early reocclusion. In comparative trials in myocardial infarction (MI) patients, TNK showed equivalent efficacy to tPA, a similar rate of intracranial hemorrhage (ICH), fewer noncerebral bleeding complications, and less need for blood transfusion.

In a pilot dose-escalating study, 75 stroke patients 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 ICH was observed during the first 72 hours after treatment. However, a dose-response relationship between TNK and neurological improvement at 24 hours was not demonstrated. Currently, TNK for the treatment of acute ischemic stroke is being investigated in a larger phase 2 trial.

Desmetoplase is 1 of 4 distinct proteases found in the saliva of the blood-feeding vampire bat Desmodus rotundus, collectively referred to as DSPAs salivary plasminogen activators (DSPAs). Desmetoplase is the α-1 variant among the DSPAs and exhibits >72% amino acid sequence identity with human tPA. Unlike human tPA, DSPAα-1 exists as a single-chain molecule, and its catalytic activity is exquisitely dependent on the presence of fibrin as cofactor. In models of arterial thrombosis, DSPAα-1 induces faster and more sustained recanalization than tPA and produces less antiplasmin consumption and fibrinogenolysis. Moreover, unlike tPA, DSPAα-1 does not enhance N-methyl-d-aspartate-mediated neurodegeneration. Desmetoplase has shown promise in 2 phase 2 ischemic stroke trials enrolling patients 3 to 9 hours after onset when a MRI diffusion–perfusion mismatch pattern is present.

Reteplase is a recombinant peptide that consists of kringle 2 and protease domains of human tPA. The long half-life of reteplase allows administration as a double-bolus injection. Reteplase produces rapid and effective coronary artery thrombolysis. Although easier to administer, reteplase did not provide an additional survival benefit compared with an accelerated infusion of alteplase in the treatment of acute MI. In a small prospective study in stroke patients, Qureshi et al demonstrated that reteplase given intra-arterially up to 9 hours after symptom onset, with or without angioplasty, resulted in a high rate of complete recanalization.

Plasmin and microplasmin, a truncated form of plasmin, are emerging fibrinolytic agents. Standard plasminogen activating drugs depend on the local availability of plasminogen to generate active, fibrin-digesting, plasmin. In contrast, plasmin and microplasmin act directly on fibrin. Because human plasmin is rapidly inactivated by circulating antiplasmin, it is potentially very useful as a local, intra-arterially applied therapeutic agent but not suitable for use as an intravenous therapeutic agent. Microplasmin retains the protease domain of plasminogen and is resistant to rapid inactivation by antiplasmin, rendering it suitable for consideration for intravenous application. In rabbit small and large clot embolic stroke models, microplasmin infusion resulted in a high rate of clot lysis and, unlike tPA and TNK, did not increase the rate of intracranial bleeding compared with control animals. Moreover, microplasmin showed nonlytic-dependent neuroprotective effects improving behavioral rating scores. Given its combined thrombolytic and neuroprotective properties, microplasmin is an attractive stroke therapy candidate.

**Glycoprotein IIb/IIIa Antagonists**

Glycoprotein (GP) IIb/IIIa antagonists potently block the platelet GP IIb/IIIa receptor, the final mediator of aggregation. GP IIb/IIIa antagonists reduce thrombus growth and prevent reocclusion after mechanical or lytic-driven recanalization. Moreover, GP IIb/IIIa antagonists have the ability to dissolve platelet-rich clots and to improve flow in coronary and cerebral microcirculation.

Abciximab is the Fab fragment of a chimeric human/mouse antibody directed against the platelet GP IIb/IIIa receptor. Abciximab administration at a bolus dose of 0.25 mg/kg followed by a continuous infusion for 12 hours, rapidly produces a profound hemostatic effect, with blockade of 80% of GP IIb/IIIa receptors, marked reduction of platelet aggregation, and prolongation of the bleeding time. The combina-
tion of abciximab, aspirin, and adjusted-dose heparin induces a high rate (up to 50%) of coronary artery recanalization. In the AbESTT phase 2b trial, 400 patients were randomized to abciximab or control within 6 hours of observed stroke onset or 3 hours of awakening with stroke; ~50% were treated 3 to 5 hours after onset. Abciximab showed a reasonable safety profile, with an ICH rate of 3.6%. A signal of potential efficacy was identified, with favorable functional outcome (modified Rankin Scale [mRS] score 0 to 1) in 48% of abciximab versus 40% of placebo patients \( (P=0.087) ^{10} \). Abciximab is being investigated currently in a phase 3 international trial (AbESTT II) enrolling 1800 patients.

Tirofiban is a tyrosine-derived nonpeptide molecule that is highly specific for GP IIb/IIIa receptor. Tirofiban appears particularly suited for platelet disaggregation, given its high targeted receptor specificity, and has a long, 1.6-hour half-life. Pilot data indicate that intravenous tirofiban can be safely administered in acute stroke patients. In an open-label pilot study, 18 patients with progressively deteriorating acute ischemic stroke were treated with weight-adjusted intravenous tirofiban for a mean period of 46 hours.\(^{11}\) No major ICH was observed, and the rate of asymptomatic ICH on CT was comparable to that observed in matched controls. Moreover, treatment with tirofiban was associated with a smaller 1-week MR infarct size compared with matched controls.\(^{12}\) SaTIS (Safety of Tirofiban in Acute Ischemic Stroke) is an ongoing phase 2 multicenter, prospective, randomized, placebo-controlled safety trial of intravenous tirofiban in 240 stroke patients with National Institutes of Health Stroke Scale (NIHSS) score of 4 to 18 and treatment instituted in an extended time window up to 22 hours after onset.

**Combined Pharmacological Approaches**

Combination pharmacotherapy strategies to expand the intravenous fibrinolysis time window beyond 3 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. Combining neuroprotective therapies with fibrinolytics may potentiate treatment benefit and extend the time window in which salvageable tissue persists to be rescued by reperfusion. 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.

**Lytics and Antithrombotics**

Combination therapy with fibrinolytic and GP IIb/IIIa agents is under wide-ranging investigation.

In a series of studies, the Dusseldorf group treated up to 37 patients within 3 hours of onset with reduced doses of intravenous tPA (typically 20 mg) and a 24-hour infusion of tirofiban. Combined therapy resulted in a high rate (68%) of middle cerebral artery (MCA) recanalization on MR angiography, greater salvage of perfusion MR–defined tissue at risk, and better clinical outcome than standard intravenous tPA.\(^{13}14\) Low rates of symptomatic ICH were observed.

A pilot study in 27 patients found combining abciximab with low-dose tPA (0.45 mg/kg) appeared safe and resulted in higher rates of MCA recanalization compared with full-dose tPA alone.\(^{15}\)

A combined thrombolytic regimen with reteplase with abciximab in MI and peripheral artery thrombosis patients yields faster, more consistent, and sustained reperfusion, and a decreased rate of distal embolization.\(^{16}\) In stroke, prospective trials under way include a 20-patient, dose-escalation safety trial of intra-arterial (IA) reteplase and intravenous abciximab administered 3 to 6 hours after onset (A Qureshi, personal communication, 2004) and a 72-patient, dose-ranging safety trial of intravenous reteplase and intravenous abciximab 3 to 24 hours after onset ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation (ROSIE/ROSIE-CT trials).

Eptifibatide is a highly selective GP IIb/IIIa antagonist currently being tested in combination with tPA within 3 hours of onset in a multicenter phase 2 dose-escalation study enrolling 100 patients (CLEAR). In addition, a randomized open-label, dose-escalation and safety trial of combined administration of tPA, eptifibatide, aspirin, and tinzaparin in stroke patients <3 hours is under way (ROSIE-2).

Argatroban is a synthetic direct thrombin inhibitor. Blocking thrombin inhibits fibrin formation in the thrombus and reduces platelet aggregation in the microcirculation. In conjunction with tPA, argatroban may enhance clot lysis, prevent reocclusion, and limit the no-reflow phenomenon in the microcirculation. Argatroban alone in human stroke appeared relatively safe, although without a strong signal of potential efficacy in the 171-patient ARGIS-1 trial. The NIH-sponsored tPA Argatroban Stroke Study (TARTS) is investigating the combination of argatroban and tPA in a pilot dose-escalating safety trial in 40 patients with a documented MCA occlusion on transcranial Doppler (TCD) within 3 hours.\(^{17}\)

**Lytics and Neuroprotectants**

Neuroprotective therapies have been shown to be more effective in animal models of ischemia when administration is followed by reperfusion rather than persisting occlusion. Further, the effects of reperfusion injury may be limited or reversed by adding neuroprotectants to reperfusion strategies. Hypothermia probably represents the most potent neuroprotectant currently under study. The COOL-AID (Cooling for Acute Ischemic brain Damage) phase 2 trial in stroke patients within 12 hours of onset demonstrated that hypothermia was well tolerated in most patients, and a trend to attenuation of diffusion-weighted imaging (DWI) lesion growth was seen in hypothermic patients. Endovascular cooling to 33°C seems to be feasible and safe in nonanesthetized stroke patients, even in those treated with thrombolysis.\(^{18}\)

By stabilizing threatened brain tissue, early neuroprotective therapy may extend the time window for subsequent effective administration of reperfusion agents. However, in most human trials performed of combined neuroprotection and thrombolytic therapy, neuroprotective interventions have...
been initiated in hospital only after the start of intravenous tPA. In the FAST-MAG (Field Administration of Stroke Therapy—Magnesium) pilot trial, paramedic initiation of magnesium sulfate neuroprotective therapy in stroke patients in the field was shown to be feasible and appeared safe. Among the 20 enrolled patients, 2 received subsequent in-hospital reperfusion interventions without hemorrhagic complication. In the NIH-funded FAST-MAG Phase 3 randomized trial, paramedics are initiating magnesium sulfate or placebo in 1298 patients within 2 hours of stroke onset and within 1 hour of onset in approximately half. The FAST-MAG Trialists anticipate that ~20% of enrolled patients will receive a Food and Drug Administration (FDA)-approved reperfusion intervention (intravenous tPA or Merci Retriever) on hospital arrival, providing substantial statistical power to explore whether hyperacute neuroprotection potentiates the benefits of subsequent reperfusion therapy.

Lytics and Vasoprotectants

Cerebral ischemia damages the cerebral vessels as well as the neuronal parenchyma, disrupting vascular integrity and predisposing to intracerebral hemorrhage. Fibrinolytic agents exacerbate this hemorrhagic risk. Administering agents that are vasoprotective along with reperfusion interventions may reduce hemorrhagic transformation rates, improve the benefit/risk ratio, and increase the permissible time window for reperfusion therapy. In preclinical studies, the rate of tPA-induced hemorrhage was markedly reduced by administration of the matrix metalloproteinase (MMP) inhibitor batimastat (BB-94) or the spin trap agent α-phenil-N-t-butyl-nitrine. The spin trap agent NXY-059 (cerovive) is currently in a phase 2 clinical trial in which the coadministration of intravenous tPA is allowed. The clinical development of MMP inhibitors, free radical scavengers, and other vasoprotective compounds for combination therapy with fibrinolytic and mechanical reperfusion interventions may substantially expand the time window in which reperfusion interventions may be undertaken safely.

Sonothrombolysis

Experimental and clinical studies have consistently demonstrated the capability of ultrasound (US) to enhance enzymatic thrombolysis. US application increases the transport of enzymes for combination therapy with fibrinolytic and inhibitors, free radical scavengers, and other vasoprotective compounds for combination therapy with fibrinolytic and mechanical reperfusion interventions may substantially improve outcome. Among 126 patients randomized to tPA plus 2-hour TCD monitoring (target group) or tPA alone (control group), symptomatic ICH occurred in 4.8% of target and 4.8% of control patients. Complete recanalization or dramatic clinical recovery at 2 hours after tPA bolus were 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. A phase 3 of the CLOTBUST trial is planned to begin in 2006. Enhancement of enzymatic thrombolysis by US may allow testing regimens with low-dose tPA to reduce the risk of ICH. The capability of microbubbles to further accelerate US-enhanced lysis in stroke patients is currently under investigation.

IA Approaches

Endovascular methods to achieve recanalization in acute ischemic stroke comprise a wide range of pharmacological and mechanical techniques. IA techniques expand the time window for reperfusion therapy by more frequently and more rapidly removing the offending thrombus than intravenous approaches and by reducing or eliminating exposure to fibrinolytic agents and their attendant bleeding risks.

IA Fibrinolysis

In local IA fibrinolysis, fibrinolytic agents are infused distal to, proximal to, or directly within thrombotic occlusions using a microcatheter delivery system. Compared with standard intravenous administration, the IA route offers several theoretical advantages, including: higher concentrations of fibrinolytic agent at the clot site; reduced systemic exposure to thrombolytics; an opportunity to carry out gentle mechanical disruption of the clot with the delivery catheter and wire; precise imaging of case-specific vascular anatomy, pathology, and collateral patterns; and exact knowledge of the timing and degree of recanalization achieved. In open clinical series, IA cerebral thrombolysis has yielded higher early recanalization rates than intravenous therapy (50% to 80% for IA and 30% to 50% for intravenous). IA fibrinolysis 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 deter catheter-induced thrombosis (potentially increasing hemorrhage risk); delay in initiation of fibrinolysis while the diagnostic angiogram is performed and the delivery microcatheter positioned (start of IA lytic infusion typically occurs 50 to 90 minutes later than start of intravenous lytic infusion); the procedure is labor- and capital-intensive; and the intervention can only be performed at tertiary and secondary hospitals capable of acute endovascular therapy. The only large-scale, multicenter, randomized clinical trial of IA fibrinolytic therapy demonstrated substantial benefit of therapy initiated up to 6 hours after onset of an M1 or M2 MCA occlusion. In the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial, the prespecified primary outcome, a good-to-excellent score on the modified Rankin Scale (mRS) of handicap (mRS ≤2), was achieved by 40% of pro-urokinase (pro-UK) patients versus 25% of control pa-
tients \((P=0.043)\). Partial or full recanalization (thrombolysis in myocardial infarction [TIMI] 2 or 3) rates 2 hours after initiation of infusion were increased markedly in the pro-UK group (66% versus 18%). However, full recanalization (TIMI 3) was infrequent even in the pro-UK group (19% versus 2% in the control group). The recanalization rates in PROACT II reflect the effects of pharmacological lysis only. Passage of a microwire to disrupt the clot and augment enzymatic lysis, although a common concomitant therapy in endovascular practice, was not permitted by the study protocol. Intracerebral hemorrhage rates at 36 hours were increased for the pro-UK group for all hemorrhages (46% versus 16%) and for symptomatic hemorrhages (10% versus 2%); however, no difference in overall mortality was observed.

Pro-UK is not available in regular practice because the results of the single PROACT II trial were insufficient to obtain FDA approval. However, multiple large case-series cohorts suggest similar efficacy and safety profiles for other, widely available fibrinolytic agents administered via the IA route, including urokinase and tPA. Based on these findings, American Stroke Association guidelines recognize IA fibrinolysis as a treatment option in select patients with large vessel occlusions, supported by evidence of intermediate weight.

**Combined Intravenous/IA Pharmacological Strategies**

A treatment strategy of combined intravenous/IA lytic therapy may combine the advantages of speed (intravenous) and definitive endovascular attack (IA). Sequential intravenous and IA fibrinolytic therapy with tPA proved somewhat disappointing in the NIH Interventional Management of Stroke (IMS) trial 1. Eighty 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, the combined intravenous/IA-treated tPA patients showed only a modest trend to improved clinical outcomes (odds ratio for global test, 1.35; CI, 0.78 to 2.37). However, alternative, nonfibrinolytic intravenous agents may be more advantageous, serving to initiate treatment and also to provide a pharmacological complement that may enhance the effectiveness of IA fibrinolysis. Preliminary studies are investigating combined intravenous G2P3 agents and IA fibrinolytics up to 6 hours after symptom onset.

**Endovascular Mechanical Therapies**

Endovascular mechanical therapies offer several distinct advantages over endovascular delivery of pharmacological fibrinolytics. Mechanical therapies typically: work more rapidly, achieving recanalization within a few minutes, rather than the up to 120 minutes required with IA fibrinolytic administration; are associated with lower intracerebral and systemic hemorrhage risk because of the avoidance of pharmacological lysis; are more effective in disposing of large clot burdens in proximal vessels, such as carotid T occlusions, where the sheer volume of clot to be digested retards pharmacological lysis; and may in general be more efficacious at achieving full recanalization.

IA mechanical interventions may be classified into the categories of endovascular thrombectomy, mechanical disruption, and augmented fibrinolysis devices.

**Endovascular Thrombectomy**

Endovascular thrombectomy devices extract occluding thrombi from the target vessel through a catheter. Subcategories include: (1) clot retrieval devices that physically grasp cerebral thrombi and pull them out of the cerebral circulation, and (2) suction thrombectomy devices that aspirate occlusive material from the vessel.

Clot retrieval devices were first developed to capture errant coils and other foreign bodies that had embolized within the cerebral circulation during endovascular procedures. A natural next step was to apply these devices to capture and remove naturally arising thromboemboli. These devices ensnare a thrombus and then withdraw it out of the body, via the guide catheter, or release it into a safer, extracerebral vascular territory. At least 3 retrieval device types have been applied to cerebral thrombi in acute ischemic stroke patients, including the Microsnare (a 90° angled wire loop; Microvena), the Neurorot (self-expanding nitinol basket; Guidiant), and the Merci Retriever X5/X6/LX (self-expanding nitinol helix; Concentric Medical). Additional devices currently FDA approved for foreign body capture that could be applied off-label to cerebral thrombi include the In-Time Retriever (4 to 6 concentric wire loops; Target) and the EnSnare (3 wire loops in tulip shape; Medical Device Technologies).

The Merci Retriever X5 and X6 devices have advanced farthest in clinical trial development and regulatory approval. In the Merci Retriever procedure: (1) 2 to 3 loops of the nitinol helix are deployed beyond the thrombus; (2) the device is retracted into the thrombus and the remaining loops deployed within the clot; (3) the helix is twisted 3 to 5 times to more fully capture the thrombus; (4) a balloon positioned proximally in the internal carotid artery is briefly inflated, blocking antegrade flow for a few seconds; and (5) while the balloon is up, the Merci Retriever and the ensnared clot are withdrawn, first into the positioning catheter and then out of the patient’s body. The Merci Retriever X5 and X6 devices were tested in the multicenter Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, a 25-site, noncontrolled, technical efficacy trial. Patients with internal carotid artery occlusion, M1 or M2 MCA occlusion, and vertebral and basilar artery occlusions were treated within 8 hours of onset. Among 121 patients enrolled, 114 underwent ≥1 (of 6 permitted) passes with a clot retriever. Partial or complete revascularization was achieved by the device alone in 54%. Successful recanalization was associated with markedly improved clinical outcomes (90-day mRS, 0 to 2 in 53% of recanalizers versus 6% of nonrecanalizers; \(P<0.0001\)). Symptomatic hemorrhage occurred in 5% of patients treated with the device alone and 24% treated with the device plus an additional rescue reperfusion intervention because of incomplete recanalization response to the device (most commonly IA fibrinolysis).
The encouraging results of the MERCI trial led the FDA in August 2004 to clear the Merci Retriever as the first device reperfusion therapy labeled specifically for use in acute ischemic stroke. The FDA labeling reads, “The Merci Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke. Patients who are ineligible for treatment with intravenous tPA (intravenous tPA) or who fail intravenous tPA therapy are candidates for treatment.” It is important to emphasize that the device is labeled for a technical outcome (removing thrombi to restore blood flow), not a clinical outcome (eg, treatment of acute ischemic stroke). Only a randomized, controlled, clinical trial of the MERCI device (such as the recently launched NIH-funded MR Recanalization of Stroke Clots Using Embolectomy [MR RESCUE] trial) or another thrombus capture device can demonstrate definitively that clot retriever therapy improves patient outcome. Vessel recanalization in acute ischemic stroke is a powerful determinant of clinical outcome and a promising candidate surrogate marker of treatment activity. In a recent meta-analysis of 62 studies enrolling 2284 stroke patients, recanalization increased the odds ratio of good outcome 5.4-fold.33 However, recanalization is not yet a fully validated surrogate that can replace clinical end points.

The next several years will undoubtedly witness rapid technologic advance in clot retrieval devices as embolectomy instruments proliferate that improve on or complement the MERCI Retriever X5/X6. Most likely, as with the MERCI Retriever, FDA will permit new clot retrieval devices to follow a rapid 510K pathway to approval, requiring only demonstration of technical efficacy in clot removal in uncontrolled trials, not clinical efficacy in improving patient outcome in controlled, randomized trials. One promising second-generation device, already being tested in humans in the Multi-MERCI clinical trial, is the Merci Retriever LX (Concentric Medical). The Merci Retriever LX has concentric helical loops with polymer filaments attached, increasing clot traction, and achieved higher recanalization rates than the X5/X6 Retrievers in preclinical studies. If technological advances in clot retrievers proceed at a pace typical of other medical devices after first in class approval, with new device designs appearing every 18 months on average, a marked increase in the available options for clot retrieval can be expected.

Suction thrombectomy devices use vacuum aspiration to remove occlusive clot in acute ischemic stroke. Compared with mechanical disruption devices, suction thrombectomy has reduced risk of causing uncontrolled thrombus fragmentation and distal embolization. Simple syringe suction applied to an endovascular catheter was successful in treating large, internal carotid artery thrombi in small case series.29 More sophisticated, vortex aspiration devices have been developed for the extracerebral circulation, using high-pressure streams to generate Venturi forces that physically fragment, draw in, and aspirate thrombi, including the AngioJet (Possis Medical), the Oasis (Boston Scientific), the Amplatz Thrombectomy Device (Microvena Corp.), and the Hydrolyzer (Cordis). The initial generation AngioJet successfully treated internal carotid and vertebrobasilar thromboses in case reports, although lack of flexibility made navigation in the intracranial circulation difficult. The NeuroJet (Possis Medical), a smaller, single-channel device, was developed specifically for the intracranial circulation, sized to enter the MCA trunk. However, in the initial feasibility and safety study in acute arterial ischemic stroke, vessel dissection was noted, and the trial was interrupted after the first 5 patients. Although modifications to device and protocol were undertaken for a successor safety trial, further development of this device for ischemic stroke has apparently now been halted.

### Mechanical Disruption of Occlusive Material

A wide range of endovascular devices are designed to mechanically fragment or completely obliterate thrombi, atherosclerotic plaque, and other vascular occlusions. Repeated passage of a micro-guidewire through a thrombus is a simple form of mechanical disruption frequently undertaken during IA fibrinolytic procedures. Laser-tipped endovascular catheters rapidly disrupt clots through conversion of photo energy into acoustic energy, resulting in clot emulsification. At least 2 systems have entered human clinical trials for acute ischemic stroke: the EPAR (Endovasix) and LaTIS (LaTIS Inc) systems. The more extensively studied EPAR system was applied to 34 patients in a multicenter safety and feasibility trial. The EPAR system alone, before patient exposure to any adjunctive lytics and stent therapies, achieved recanalization in 35% (8 of 23) of patients receiving any firing of the laser and 57% (8 of 14) of patients receiving complete lasing per protocol14(Angsar Berlis, personal communication, 2004). No adverse effects directly attributable to lasing were noted, but 3 patients had symptomatic ICH. These results suggest that endovascular photoacoustic clot disruption holds promise as a mechanical recanalization strategy in acute stroke.

Primary intracranial angioplasty is a promising endovascular reperfusion strategy in select clinical circumstances. In acute MI, primary angioplasty and stenting are superior to fibrinolytic therapy, yielding higher recanalization rates and better long-term outcomes. Several case series have reported success with acute percutaneous balloon angioplasty for ischemic stroke.35 Angioplasty appears particularly useful in patients with intracranial atherosclerotic lesions and supervening in situ thrombi. In these lesions, as in the coronary bed, angioplasty in part achieves recanalization through controlled cracking and dissection of underlying atherosclerotic lesions on which supervening thrombus has developed. However, many cerebral occlusions are attributable to thrombi of proximal origin that embolize to lodge in recipient cerebral vessels without extensive underlying calcified atherosclerosis. These spongy cerebral clots often bounce back into an occlusive position after balloon angioplasty. As a result, primary cerebral angioplasty has tended to be less successful when applied in white populations (among whom thromboembolism to intracranial vessels is a frequent stroke mechanism) than in Asian populations (among whom in situ intracranial atherothrombosis is a frequent stroke mechanism).28-29 It may be speculated that primary stenting will better maintain patency than angioplasty without stenting when the target cerebrovascular lesion is an embolized
thrombus. If so, continued advances in the development of intracranial stenting technology may expand the applicability of acute cerebral angioplasty to a broader range of patients.

**Augmented Fibrinolysis**

Several mechanical techniques may enhance pharmacological fibrinolysis. Passage of a micro-wire through an occlusion during IA fibrinolytic procedures is a form of augmented fibrinolysis, not only directly disrupting the clot but also increasing penetration of fibrinolytic agent throughout the target thrombus.36 Endovascular US techniques to enhance enzymatic, intra-arterially delivered fibrinolytic agents are being developed in a manner complementary to external US techniques to enhance intravenously administered fibrinolytics. The EKOS MicroLysUS infusion catheter (EKOS Corp) system for augmented thrombolysis was tested in a small, multicenter safety and feasibility trial within 6 hours after onset of anterior and 13 hours of posterior circulation ischemia. Partial or complete recanalization was achieved within 1 hour of therapy start in 8 of 14 (57%), and symptomatic hemorrhagic transformation occurred in 2 of 14 (14%).37 The Interventional Management of Stroke Trialists are currently investigating a strategy of upfront intravenous tPA followed by IA tPA administered via the EKOS catheter for lytic augmentation.

**Combined Pharmacological—Endovascular Mechanical Strategies**

Early experience with this wide range of emerging endovascular interventions suggests that combined pharmacological and endovascular mechanical therapies will often be required to achieve optimum reperfusion.28 Mechanical devices are currently too bulky to pass into distal vessels and often fragment proximal clots, causing pieces to embolize distally. Cleanup IA fibrinolysis directed at distal residua will often be a consideration in patients treated with mechanical devices if it can be pursued with low additional risk. Complementary treatment approaches may be needed to address occlusive lesions of mixed composition. Initial application of fibrinolytics may lyse a small supervening thrombus superimposed on a near-occlusive atherosclerotic lesion, but follow-up angioplasty will be needed to maximize patency and avert early reocclusion. “Rescue” therapy with ≥1 modalities after initial therapy has failed will often be desirable. An occlusion initially thought to be an embolic thrombus but unresponsive to thrombus treatments (eg, clot retrievers, aspiration, and laser) should suggest underlying atherosclerosis and the need for “rescue” angioplasty. Conversely, a vessel repeatedly reoccluding after angioplasty may suggest spongy thrombus in a near-normal underlying vessel and the need for “rescue” fibrinolytics, clot retrieval, or other appropriate intervention. Tandem lesions may require tandem treatments (eg, primary stenting of an extracranial internal carotid stenosis or occlusion to permit access of a thrombus capture device or IA fibrinolytic delivery catheter to an artery-to-artery embolus lodged in the MCA). Tailored approaches chosen from a range of mechanical and pharmacological options likely will be required to achieve optimum recanalization rates, always bearing in mind that the cerebral vasculature is fragile and the amplitude of mechanical energies and intensity of pharmacological therapies delivered to break up thrombi will be limited by the need to protect vessel wall integrity.

**Using Multimodal Imaging to Extend the Reperfusion Treatment Time Window**

The duration of the ischemic penumbra varies widely from patient to patient. Late reperfusion therapy is likely to benefit individuals in whom substantial salvageable tissue still persists beyond the first few hours after symptom onset but not benefit, and possibly harm, patients who have completed their infarction. Multimodal MR and CT imaging protocols render a multidimensional depiction of the cerebral ischemic process: distinguishing infarct from hemorrhage; delineating irreversibly injured infarct core, still salvageable penumbra, and unthreatened regions of benign oligemia; identifying propensities to hemorrhagic transformation; and ascertaining large vessel stenoses and occlusions, all in just 5 to 20 minutes of table time (Figure).38,39 These protocols poten-
Provisional Multimodal MR/CT Algorithm for Selecting Patients for Late (>3 hours) Reperfusion Therapies

<table>
<thead>
<tr>
<th>Very favorable candidate for intravenous or IA therapy</th>
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<tbody>
<tr>
<td>Distal M1 or proximal M2 MCA occlusion, beyond takeoff of lenticulostriate branches + substantial visualized penumbra*</td>
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<tr>
<td>Favorable candidate for intravenous or IA therapy</td>
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<tr>
<td>Proximal M1 MCA occlusion + substantial visualized penumbra</td>
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<tr>
<td>Somewhat favorable candidates for therapy</td>
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<tr>
<td>Distal internal carotid artery occlusion + substantial visualized penumbra (IA&gt;=IV)</td>
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<td>Distal MCA/ACA branch occlusion + severe functional deficit + substantial visualized penumbra (IV)</td>
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<tr>
<td>Penetrator occlusion + severe functional deficit + substantial visualized penumbra (IV)</td>
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<td>Avoid fibrinolytic therapy; IA mechanical therapy may be considered but benefit/risk ratio reduced</td>
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<tr>
<td>Large infarct core, more than one third of MCA territory (DWI change on MR, collapsed CBV on CT), but substantial visualized penumbra</td>
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<tr>
<td>Avoid therapy</td>
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<tr>
<td>No substantial visualized penumbra</td>
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*Methods for identifying when substantial penumbral tissue is present are rapidly evolving. Simple current approaches are MR PWI-DWI mismatch or CT CTP-collapsed CBV mismatch >=20% in diameter on slice with largest lesion. Multivariate predictive equations offer greater accuracy but are less widely accessible.

It is important to emphasize that in any conceivable circumstance, it will always be crucial to institute therapy as soon as possible. For early and late treatment window patients, there will always be a tradeoff between more information and more dead brain. Moreover, within the first 1 to 2 hours of onset, virtually all patients harbor substantial penumbra, whereas among late-presenting patients, a steadily decreasing proportion evidences persisting penumbra. Opening up late treatment time windows for select patients through multimodal imaging is a complementary strategy to achieving early treatment times for all early presenting patients.

Multiple current clinical trials are refining or incorporating MR strategies to expand patient eligibility for reperfusion therapy, including studies: (1) identifying candidate MR measures for patient selection (no internal control group, all patients treated irrespective of entry MR pattern); (2) validating prespecified MR measures for patient selection (randomized, controlled design, all patients enrolled irrespective of entry MR pattern); and (3) already using MR measures for patient selection, although these measures have not yet been fully validated (randomized, controlled design; only patients exhibiting MR pattern felt predictive of good treatment response enrolled).

Identifying Candidate MRI Algorithms to Select Patients for Late Reperfusion Therapy

DEFUSE (Diffusion-weighted imaging Evaluation For Understanding Stroke Evolution) is an NIH-funded, multicenter, uncontrolled pilot study investigating whether specific DWI-perfusion-weighted imaging (PWI) profiles predict a favorable clinical response to intravenous tPA administered 3 to 6 hours after stroke onset. Patients with a clinical diagnosis of ischemic stroke causing measurable moderate-to-severe neurological deficit (NIHSS score >5) are included, regardless of MR PWI-DWI pattern.

Validating MRI Algorithms

The randomized EPITHET (Echoplanar Imaging Thrombolysis Evaluation Trial) is an ongoing double-blind, randomized, multicenter study with a planned enrollment of 100 patients. EPITHET aims to determine whether the extent of the ischemic penumbra apparent on perfusion–diffusion MRI identifies patients who will benefit from intravenous tPA 3 to 6 hours after stroke.

MR RESCUE is an ongoing, NIH-funded, multicenter, randomized clinical trial with a planned sample size of 120 patients. The trial tests the hypothesis that the presence of substantial ischemic penumbral tissue visualized on diffusion–perfusion MRI identifies patients most likely to respond to Merci Retriever mechanical embolectomy up to 8 hours from symptom onset.

Using Multimodal MRI Algorithms to Select Patients for Late Reperfusion Therapy

The DIAS (Europe/Australia) and DEDAS (United States/Canada) Trials are randomized, multicenter, placebo-controlled, dose-escalating trials assessing the safety and thrombolytic efficacy of intravenous desmoteplase in MRI-selected patients with acute ischemic stroke between 3 to 9 hours after stroke onset. Patients are eligible if MRI within 8 hours shows ongoing hyperperfusion (PWI abnormality ≥2 cm in diameter in the hemispheric gray matter) and still salvageable penumbra (PWI/DWI mismatch >20%). The preliminary results of DIAS appear to validate the strategy of treating late-presenting, imaging-selected patients with intravenous fibrinolysis. A dose-response relationship was demonstrated between desmoteplase and reperfusion. At the apparent optimal dose of 125 μg/kg, reperfusion (PWI reduction ≥30% or TIMI change ≥2 post-thrombolysis) occurred in 71% of patients (versus 22% in placebo) and excellent clinical outcome in 60% (versus 18% in placebo; S. Warach, International Stroke Conference San Diego, Calif, 2004). The rate of symptomatic intracerebral hemorrhage was low (3.3%) in this dose range (90 and 125 μg/kg). Safety and efficacy appeared independent of the time window. A pivotal trial with 125 μg/kg IV desmoteplase in imaging-selected patients in the 3- to 9-hour window is planned.

The ROSIE trial is a phase 2 safety and dose-ranging study of combined reteplase and abciximab initiated 3 to 24 hours after stroke onset. Leading entry criteria are NIHSS score ≤16, a perfusion MR deficit, and absence of a DWI abnormality more than one third of the MCA territory. Patients receive abciximab alone or abciximab plus 1 of 4 tiers of reteplase.

Clinical-Diffusion Mismatch

Clinical-DWI mismatch (CDM) represents a new diagnostic approach that can extend MR identification of persisting
penumbra to hospitals that have diffusion but not perfusion MR imaging. Because most ischemic brain tissue is clinically symptomatic, stroke severity as measured by the NIHSS score correlates with the extent of hypoperfused tissue (PWI abnormality). CDM is defined as an NIHSS score ≥8 and ischemic volume on DWI ≥25 mL. The NIHSS score of ≥8 has been associated with cortical perfusion deficits and high rate of neurological deterioration. In 166 patients imaged within 12 hours of hemispheric ischemic stroke onset, CDM was found in 87 (52%). The frequency of CDM decreased as time from onset increased, being 74% at <3 hours, 48% from 3 to 6 hours, and 46% from 6 to 12 hours. The presence of CDM was associated with a higher rate of early neurological deterioration, greater DWI lesion growth at 72 hours, and larger infarct volume on T2-weighted MRI at day 30. However, because the NIHSS score underestimates infarct volume in the right hemisphere, the CDM definition may be less sensitive to estimate penumbra tissue in right-sided lesions. Prospective validation of the CDM definition is needed to determine its reliability to rapidly identify patients with tissue at risk as candidates for reperfusion strategies.

Selection Based on Multimodal CT Criteria
Novel CT techniques also show great promise as tools to stratify later-presenting patients into groups likely and not likely to benefit from reperfusion. CT angiography (CTA) is a well-established technique to identify acute vascular occlusions. Several CT techniques are now available to image tissue perfusion, including perfusion CT (PCT), CTA source image analysis, and xenon-CT. Of these, particularly great potential is shown by dynamic PCT, in which images are acquired during first pass of a standard iodinated contrast bolus.

PCT cerebral blood flow (CBF) maps distinguish penumbra from benign oligemia by differentiating regions with moderate versus mild reductions in blood flow. PCT cerebral blood volume (CBV) maps distinguish infarct core from penumbra by delineating regions with advanced tissue injury, loss of autoregulation, and vascular collapse, evident as markedly decreased CBV. Accordingly, PCT offers an analogue to the MR mismatch model of core and penumbra, with regions of collapsed CBV representing core and regions with reduced CBF but preserved CBV (CBF-CBV mismatch) representing penumbra. Penumbral regions identified by CT CBF-CBV mismatch correlate well with penumbral regions identified by MR DWI-PWI mismatch when both studies are obtained in the same acute stroke patients.

Multimodal CT techniques are just beginning to be applied in formal clinical trials and advanced clinical practice to extend treatment time windows by selecting patients for late reperfusion. Compared with MR, multimodal CT has the disadvantages of less coverage of brain tissue (interrogating only 2 to 4 slices at present), use of iodinated contrast with allergic and renal toxicity, and poor visualization of infratentorial tissues attributable to bone artifact. However, CTA/PCT has the advantages of more rapid patient positioning and scan acquisition, wider availability of hardware and staffing, and an easier upgrade path to implementation for many hospitals, building on the existing infrastructure of emergency CT scanners.

Conclusions
The ideal toward which reperfusion therapies for stroke strive is to achieve complete and lasting vessel patency, as rapidly as possible, in all patients harboring salvageable tissue, with no risk of hemorrhagic transformation. This review has surveyed >45 distinct, promising approaches to extending reperfusion in cerebral ischemia currently under investigation in human clinical studies. Areas of advance include novel pharmacological classes, novel agents within classes, novel mechanical devices, novel imaging selection paradigms, and novel combinations of these techniques. Further development of these therapies will require innovations in clinical trial design to meet the emerging challenges of testing combination therapies, device therapies, and therapies tailored to individual pathophysiology while retaining definitive phase 3 trials as the gold standard for assessing treatment benefit. If studied correctly, therapeutic reperfusion promises to emerge as a treatment strategy of remarkable power and scope for rescuing patients experiencing acute brain ischemia, applicable within and beyond the 3-hour time window.

References


Extending Reperfusion Therapy for Acute Ischemic Stroke: Emerging Pharmacological, Mechanical, and Imaging Strategies
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