Published in final edited form as:
Stroke. 2012 February ; 43(2): 591–598. doi:10.1161/STROKEAHA.111.617902.

Adjunctive and alternative approaches to current reperfusion therapy

Andrew D. Barreto, MD[1,*] and **Andrei V. Alexandrov, MD**[2]

[1]Department of Neurology, Stroke Program; The University of Texas-Houston Medical School, Houston, Texas

[2]Comprehensive Stroke Center, Department of Neurology; University of Alabama-Birmingham, Birmingham, Alabama

Abstract

Background and Purpose—Current ischemic stroke reperfusion therapy consists of intravenous (IV) thrombolysis given in eligible patients after review of a non-contrast CT scan and a time-based window of opportunity. Rapid clot lysis has a strong association with clinical improvement, but remains incomplete in many patients. This review appraises novel adjunctive or alternative approaches to current reperfusion strategies being tested in all trial phases.

Summary of Review—Alternative approaches to current reperfusion therapy can be separated into four main categories: 1) combinatory approaches with other drugs or devices; 2) novel systemic thrombolytic agents; 3) endovascular medical or mechanical reperfusion treatments and 4) non-invasive or minimally-invasive methods to augment cerebral blood flow and alleviate intracranial blood flow steal.

Conclusions—Reperfusion treatments must be provided as fast as possible in patients most likely to benefit. Patients who fail to rapidly reperfuse may benefit from other strategies that maintain collateral flow or protect tissue at risk.

Keywords

reperfusion; acute stroke; thrombolysis; endovascular treatment; adjunctive treatment

Introduction

Reperfusion of ischemic brain remains the first target of acute stroke treatment. Timely reperfusion is paramount, and amplification of the only proven treatment, intravenous tPA, or other alternatives are under intense investigation. Unlike heart disease, stroke has been a more difficult challenge to develop and adopt adjunctive therapies due to many factors such as: a lower-resistance vascular bed, higher risk of post-treatment tissue damage and hemorrhage, difficulty in rapid diagnosis (i.e., posterior circulation location) and variability in disease pathogenic mechanisms.

Still today, the standard, but under-utilized, reperfusion strategy of IV-tPA relies upon a non-contrast head CT and a strict time window. Although alteplase medication labeling lags

[*]Correspondence: 6431 Fannin Street, Room MSB 7.124, Houston, Texas 77030. 713.500.7002 (office) 713.500.0692 (fax), andrew.d.barreto@uth.tmc.edu.

Conflict of Interest

Dr. Barreto served as PI for North American centers in the TUCSON trial funded by ImaRx Therapeutics. Dr. Alexandrov serves as consultant to Cerevast Therapeutics (Redmond, WA).

behind societal position statements, clinical practice has already incorporated the extended time window of 4.5 hours.[1, 2]

Intravenous tPA effectiveness largely depends on thrombus location and burden. For instance, large proximal clots such as the terminal internal carotid artery (TICA) occlusion are less susceptible to IV-tPA alone.[3, 4] Saqqur et al. used transcranial Doppler (TCD) ultrasound to monitor the 2-hour response of IV-tPA: complete recanalization was highest (44.2%) in distal middle cerebral artery (MCA) occlusions but dropped off dramatically in more proximal locations: 30% proximal MCA and only 5.9% in the TICA.[4] However, the presence of a large proximal intracranial occlusion should not be viewed as insurmountable obstacle and contraindication to IV-tPA within approved time window.

While improvements in stroke care delivery maximize of the chance for stroke patients to receive reperfusion therapy, adjunctive techniques are being tested to improve upon low IV-tPA reperfusion rates. Some approaches are low-tech, but broadly applicable at any-level stroke center. Conversely, other strategies are invasive, labor and resource intensive and could most likely be performed predominantly at comprehensive stroke centers. This review highlights emerging therapies which aim to enhance IV thrombolysis or maximize tissue perfusion in patients who either are not eligible or have failed IV treatment(Table). Neuroprotective strategies or medical therapies which do not directly attempt to aid in thrombus lysis will not be discussed.

Combined Pharmacological Approaches (Lytic + Antithrombotic agents)

Direct Thrombin Inhibition

The thrombin inhibitor Argatroban (GlaxoSmithKline, Philadelphia, PA), directly and selectively inhibits the action of free and clot-associated thrombin. Safety has been demonstrated with and without thrombolytics or aspirin in patients with acute myocardial infarction(MI).[5] In animal stroke models, argatroban safely augments the benefit of tPA by improving flow in the microcirculation, increasing the speed and completeness of recanalization, and preventing reocclusion.[6–8] The Argatroban Anticoagulation in Patients with Acute Ischemic Stroke (ARGIS-1) study showed that argatroban (mean doses of 1.2 and 2.7 μg/kg per minute) given within 12 hours of ischemic stroke provides safe anticoagulation without an increase in intracerebral hemorrhage (ICH).[9] No clinical benefit was observed but it should be noted that patients did not receive tPA treatment.

The Argatroban TPA Stroke Study (ARTSS), a pilot safety study of full dose IV-tPA(0.9mg/kg)+Argatroban recently completed enrollment. Eligibility included patients aged 18 to 85 years admitted within 4.5 hours of stroke onset and meeting the criteria for intravenous-tPA therapy. Patients were also required to be within the NIH stroke scale (NIHSS) limits of 5–20 on the left hemisphere and 5–15 on the right hemisphere, have a proximal intracranial arterial occlusion measured by TCD or CT-angiogram (CTA), and an INR ≤1.5. Subjects received IV-tPA+argatroban: 100 μg/kg bolus started during the tPA infusion then followed by a 1 μg/kg infusion for 48 hours. Argatroban was titrated to a target partial thromboplastin time (PTT)=1.75 times baseline. The first 15 patients were enrolled at the 1μg/kg dosage and 2 patients experienced symptomatic ICH (sICH) (13%, 95% confidence interval: 4–48%). However, at 2-hours, there was a non-significant trend towards greater rates of complete recanalization compared to historical, IV-tPA treated patients from the CLOTBUST study (43% vs. 13%, P=0.25).[10, 11] Before exploring the safety of higher-dose Argatroban (3μg/kg titrated to goal PTT of 2.25 times baseline), the FDA required an additional 50 patients enrolled at the 1.75 dose.

Final results of the ARTSS study (n=65) were presentedat the 2011 International Stroke Conference(ISC). The combination appeared to be safe with 4 (6.2%) ICH cases: 3 symptomatic (4.6%) and 2 PH-2 (3.1%) hemorrhages (one patient had both a PH-2 and a sICH). Further, rates of complete recanalization at 2-hours were now significantly higher in Argatroban-treated patients when compared to the CLOTBUST trial controls(30 vs. 13%, *P*=0.03). The authors concluded that the combination treatment warrants further study.

Low Molecular Weight Heparin (LMWH)

In the setting of acute MI, the combination of tPA and heparin is superior to tPA alone due to increased patency rates and reduced reocclusion. The combination of LMWH and IV-tPA was tested in an open-label pilot safety study by Mikulik and colleagues.[12] A total of 60 patients were treated with either IV-tPA+LMWH (Early group -LMWH started immediately after thrombolysis) or delayed LMWH began 24 hours (Standard group). Nadroparin 2,850 IU was given every 12 hours (dose higher than for deep venous thrombosis (DVT) prophylaxis, but lower than pulmonary embolism or DVT treatment regimen). The median NIHSS score was 13 in each group. No baseline or follow-up vessel imaging was performed for purposes of assessing reperfusion. Symptomatic ICH occurred in 8.6% of the early group 4% of the standard group (*P*=NS). Although not statistically significant, more patients treated with early anticoagulation experienced favorable outcome (modified Rankin Scale score (mRS) of 0–1) at 90 days (45.7% versus 36%), and this trend may warrant further studies.

Acetylsalicylic Acid

The formation of an occlusive thrombus is dependent on two interacting different mechanisms: fibrin formation and platelet activation. Therefore, combining fibrinolytic and antiplatelet medications theoretically should enhance recanalization and conceivably reduce rates of reocclusion. In fact, antiplatelet medications are indicated in patients who receive fibrinolytic therapy for MI and are synergistic for reducing mortality.[13, 14]

Intravenous acetylsalicylic acid (ASA)given concurrently with IV-tPA is currently being studied in a randomized controlled Phase 3 efficacy trial – the ARTIS study.[15] The ARTIS study is delivering 300mg of IV-ASA within 1.5 hours of the tPA bolus and is powered to detect a 10% absolute reduction in poor outcome (mRS at 90 days of 3–6) compared to IV-tPA alone. Any patient who receives IV-tPA per local protocol is eligible. As of May 2010, 361 of the 800 patients have been included.[16] Vessel recanalization post-treatment is not a pre-planned secondary outcome.

Glycoprotein IIb/IIIa Inhibitors

The cascade of platelet aggregation terminates in the glycoprotein (GP) IIb/IIIA receptor. GPIIb/IIIa inhibitors are commonly used in high-risk acute MI and to prevent percutaneous coronary stent occlusion. Combination GP IIb/IIIa inhibitors plus IV-thrombolysis resulted in higher rates of TIMI 3 reperfusion (compared to non-GPIIb/IIIa arms) in phase II studies.[17] However, when tested in a phase III trial of 16,588 patients with acute ST-elevation MI, combination low-dose reteplase+abxicimab versus standard-dose reteplase, there was no difference in the primary endpoint of 30-day mortality.[18] In the setting of ST-elevation MI, GP IIb/IIIa inhibitors are currently predominantly used as an adjunct treatment during percutaneous coronary intervention.

For acute ischemic stroke treatment, GPIIb/IIIa inhibitors as monotherapy have shown mixed results. A phase II study (the SaTIS study) randomized 250 patients to a 48 hour infusion of tirofiban versus placebo.[19] There were no bleeding concerns, but no early neurological changes attributable to the drug were found. However, the 6-month mortality

favored the tirofiban group. Abciximab (phase III AbESTT II trial) was tested in ischemic stroke patients who could be treated within 5 hours of symptom onset.[20] Unfortunately, due to an unfavorable benefit-risk profile, the study was terminated early. A similar fate befell a study of 150 patients who received tirofiban or placebo for 72 hours -the study was halted due to lack of a trend for difference between the two groups.[21] In vitro and in vivo experimental studies suggest that combination therapy (fibrinolytic agent plus GPIIB/IIIA inhibitor) provide more complete lysis than fibrinolytics alone.[22, 23] The combination was evaluated in a multicenter phase 2 study, The Combined Approach to Lysis Utilizing Eptifibatide and tPA in Acute (CLEAR trial).[24] Ninety-four 0–3 hour ischemic stroke patients were randomized into 3 different arms: IV-tPA (0.9mg/kg) alone or two different combination arms of low-dose IV-tPA (0.3mg/kg and 0.45mg/kg)+eptifibatide (75 μg/kg bolus followed by 0.75μg/kg/minute infusion for 2 hours) with combination treatment given in 69 patients (3:1 randomization to combination arms). Unfortunately, pre-and post-treatment vessel imaging was not performed so reperfusion could not be assessed. Safety of the combination was acceptable as only one sICH occurred in the combination group (1.4%). Although not designed or powered to assess clinical outcomes, the authors reported a paradoxical trend towards increased efficacy of the tPA-alone group compared with the combination arms. Despite this, since safety of the drug combination was deemed adequate, investigators have embarked on a second phase 2, 2-arm study comparing a higher dosage of tPA (0.6mg/kg) + eptifibatide versus standard (0.9mg/kg) dose IV-tPA – the CLEARER trial.[25] Planned enrollment is 126 patients with 5 to 1 enrollment into the experimental arm.

The ROSIE (ReoPro Retavase Reperfusion of Stroke Safety Study -Imaging Evaluation) study was an open-label safety evaluation of combined abciximab (0.25mg/kg bolus followed by a 0.125 mcg/kg/min infusion for 12 hours) with 5 different dosages of the intravenous fibrinolytic reteplase (2.5, 5, 7.5, or 10 Units). All patients presented between 3 and 24 hours after stroke onset and had MRI perfusion-diffusion mismatch. Interim results of 34 patients enrolled were presented at the 2006 ISC.[26] Safety was evaluated by incidence of sICH or major systemic hemorrhage within 48 hours of treatment. A response of the combination was defined as complete reperfusion as seen on brain MRI within 24 hours. Six percent of patients experienced bleeding – one sICH and one gastrointestinal hemorrhage, neither of which were fatal. Reperfusion occurred in 33% in the abciximab monotherapy group, 40% in the 2.5 U group, 45% in the 5 U group, 58% in the 7.5 U group, and 50% for those in the 10 U group. Due to safety concerns in the AbESTT-II trial, study completion was interrupted and final publication of results of ROSIE are still pending.

Combined Non-invasive Mechanical Approaches

Sonothrombolysis

Ultrasound potentiates the effect of tPA in-vivo by temporarily separating strands of fibrin allowing for more tPA to reach binding sites due to enhanced plasma streaming. The energy delivered by FDA-approved diagnostic equipment (2-MHz frequency) augmented the effects of tPA in the phase 2 CLOTBUST study (Combined Lysis Of Thrombus in Brain ischemia Using transcranial ultrasound and Systemic TPA).[10] The term sonothrombolysis is used to describe the ultrasound-associated clot lysis. Two-hours of 2-MHz TCD aimed at the worst residual flow signal along the proximal MCA was safe (i.e., no increase in sICH) and resulted in a significant increase in the percentage of patients with complete MCA recanalization (38% versus 13%, P=0.002). Although not powered for clinical efficacy, there was a non-significant 13% absolute increase in 3-month mRS 0 or 1 the ultrasound arm (42% versus 29%, P=0.2).

After CLOTBUST, several sonothrombolysis studies followed. Some utilized lower frequencies of ultrasound which proved to have unsafe bioeffects and others combined

intravenous microbubbles with the ultrasound and tPA in an attempt to further enhance clot dissolution.[27] Microbubbles (also referred to as microspheres) oscillate in shape and can also cavitate releasing more energy along tissues exposed to ultrasound. The resultant momentum of bubble movement can increase residual flow around and through the thrombus and facilitate its mechanical degradation, thus promoting recanalization. In 2005, Molina et al published their safety trial of galactose-based microbubbles, 2-MHz ultrasound and tPA.[28] Three different arms were tested in 0–3 hour MCA strokes (n=111): tPA alone; tPA+ultrasound and tPA+ultrasound+microbubbles. The microbubble arm proved to be safe (no increase in sICH) and resulted in a remarkably high 2-hour complete recanalization rate of 54%. The TUCSON (Transcranial Ultrasound in Clinical SONothrombolysis) trial also tested the safety of tPA, ultrasound and escalating doses of intravenous microspheres (a lipid-based shell which is more consistent in size and resistant to transpulmonary passage).[29] The study was terminated in the 2nd dose tier after the occurrence of 3 sICH (27%). However, tier one (one vial of microspheres) experienced no safety issues and 67% complete recanalization.

A recent comprehensive review and meta-analysis identified 6 randomized (n=224) and 3 non-randomized (n=192) sonothrombolysis stroke studies.[30] When compared to IV-tPA treatment alone, the pooled rate of sICH in randomized studies did not demonstrate a safety concern. Complete recanalization rates were higher in patients receiving combination of TCD with tPA 37.2% (95% CI, 26.5%–47.9%) compared with patients treated with tPA alone 17.2% (95% CI, 9.5%–24.9%). In 8 trials of high-frequency (i.e., 2-MHz) ultrasound-enhanced thrombolysis, ultrasound with or without microspheres was associated with a higher likelihood of complete recanalization (pooled OR, 2.99; 95% CI, 1.70–5.25; P=0.0001) when compared to tPA alone. Results of this review provide scientific rationale for continued studies of sonothrombolysis including an efficacy trial.

In order to address a frequent concern regarding TCD ultrasound enhanced lysis, namely it's operator-dependence, an operator-independent device has been developed. Through NIH-funding, the safety of a novel, hands-free device has been tested in stroke-free volunteers and is currently in clinical testing.[31] The device requires no ultrasound training and is placed on the head following anatomical landmarks. Eighteen different 2-MHz probes (6 on each TCD skull window) are sequentially activated at the same energy level as the original CLOTBUST study and targeted at the proximal intracranial vessels. Successful operator-independent ultrasound delivery makes a larger phase III efficacy trial of sonothrombolysis feasible.[32]

Novel Thrombolytics

Tenecteplase

Tenecteplase (TNK), a structurally modified form of native tPA (with increased half-life and fibrin specificity), has undergone both pre-clinical and clinical studies in ischemic stroke. TNK is delivered in a bolus with no infusion necessary. Already approved for MI, the drug has an improved safety profile with lower systemic bleeding complications. TNK is also 14 times more fibrin specific and is more resistant to degradation from plasminogen activator-1 compared with tPA.[33]

Clinical stroke studies of TNK began in 1999 when Haley et al performed a pilot, dose-escalation safety study in 88 stroke patients.[34] All patients were treated within the 0–3 hour window using identical NINDS-tPA study inclusion/exclusion criteria. Four dosage tiers were tested: 0.1, 0.2, 0.4 and 0.5mg/kg (maximum 100mg) with 25 patients treated at each dose with the exception of the 0.5 tier that was stopped after 2/13 patients suffered sICH. No concurrent controls with alteplase were obtained making comparisons for clinical outcomes

purely historical. Authors concluded that TNK at doses of 0.1–0.4mg/kg were safe in ischemic stroke. The next trial was NIH funded and utilized a design that facilitated a seamless transition from Phase II to III provided a promising dose was found with adequate safety.[35] The trial began as a Phase IIb randomized, double-blind trial that sought the optimal dose of tenecteplase: 0.1, 0.25 or 0.4mg/kg. The control arm was alteplase at standard dosing and all patients were treated within the 0–3 hour window. The study utilized a combination score which balanced sICH with early (24-hour) neurological improvement and resulted in the dropping of the 0.4mg/kg dose after only 73 patients had been enrolled-3 of 19 (15.8%) patients experienced sICH. The 2 lower doses were continued, but unfortunately due to slow enrollment the study was terminated prematurely. Investigators were unable to explore futility or treatment effects in the other arms with so few patients (n=31), though TNK may still be a candidate for further trials in stroke.

Desmoteplase

Vampire bat (*Desmodus rotundus*) saliva contains a plasminogen activator (desmoteplase) which has a significantly greater amount of fibrin specificity compared to tPA. The DIAS study (Desmoteplase In Acute Stroke) explored this new agent in stroke patients in an extended window.[36] Patients were treated between 3 and 9 hours from symptom onset and selected using MRI criteria that were thought to indicate evidence of salvageable tissue (diffusion/perfusion mismatch) with 104 patients enrolled in a double-blind, placebo-controlled safety and dose-escalation study. Only 1 of the 57 desmoteplase treated patients suffered a sICH (dosage = 90 μg/kg). Reperfusion rates (on follow-up MRI imaging) verified the thrombolytic effects of the drug (71.4% in the high-dose arm compared to 20% in placebo). There was a dose-dependent increase in the rates of favorable clinical outcome: 13.3%, 46.7%, and 60% of patients in the 62.5 μg/kg, 90 μg/kg, and 125 μg/kg desmoteplase groups, respectively, compared with 18.2% in the placebo group. DIAS produced promising results on two fronts: safety and efficacy of a new thrombolytic and imaging-selected thrombolysis at an extended time window.

The DEDAS study (Dose Escalation of Desmoteplase for Acute Ischemic Stroke) was an extension of the DIAS study that focused on the two most promising doses 90 μg/kg and 125 μg/kg. Again, DEDAS was a double-blind, placebo-controlled safety and dose-escalation study (3–9 hours from symptom onset) performed in 37 patients.[37] No sICH occurred. MRI reperfusion was the highest with the 125 μg/kg dose and correlated with good clinical outcome. Authors concluded that DIAS and DEDAS provided evidence that 125 μg/kg of desmoteplase is safe and effective for MRI-guided thrombolysis at an extended window.

DIAS-2 was the logical next step to the development of desmoteplase in acute ischemic stroke – a pivotal phase III clinical trial. DIAS-2 was a prospective, double-blind, single-bolus study investigating the efficacy and safety of 2 doses of desmoteplase, 90 and 125 μg/kg, given as an intravenous bolus.[38] Patients were eligible for DIAS-2 if they could be treated within 3 and 9 hours after the onset of stroke symptoms, had a NIHSS of 4 to 20, and had a distinct ischemic penumbra of at least 20% established by MRI DWI/PWI mismatch or perfusion computed tomography (CTP). The primary outcome was clinical improvement at day 90, defined as having achieved all of the following: an improvement in NIHSS score of 8 points or more (or an NIHSS score of ≤ 1), Barthel Index score of 75 to 100, and a mRS 0–2. DIAS-2 targeted an aggressive absolute treatment effect of 25%. Between 2005 and 2007, 193 patients were randomized and 186 received treatment (n=57 in 90 μg/kg arm; n=66 in 125 μg/kg and n=63 placebo). Interestingly, only 30% of patients had a visible occlusion on baseline imaging. Unfortunately, despite adequate safety results (sICH rates of 3.5 and 4.5% in low and high-dose arms, respectively) there was no difference in the primary clinical outcome. Authors postulated a few different interpretations regarding the discrepant results between DIAS-2 and DEDAS/DIAS-1: a) milder strokes in DIAS-2

patients (median of 9 vs. 11); b) lower rates of TIMI 0 or 1 vessel occlusion (26% vs. 54%); c) use of CTP in DIAS-2 whereas MRI was the sole imaging in prior studies. Post-hoc analysis revealed an 18% and 9% clinical response rate in patients with a TIMI 0–1 occlusion in the low and high-dose arms, respectively. Response to treatment in this analysis has spurred the design of the next DIAS study (currently ongoing) that only includes patients with arterial occlusions.

Plasmin

Plasmin is the final common pathway of traditional thrombolytics (so called direct-acting fibrinolytic). Due to the short half-life and rapid inactivation (within seconds) of by α2-antiplasmin, plasmin is more suitable for local (intra-arterial therapy) administration. Marder and colleagues tested plasmin in a rabbit stroke model of thrombin-induced MCA occlusion.[39] Arterial recanalization on angiography was successful in all 9 rabbits infused with plasmin. Conversely, none of the 3 control rabbits recanalized spontaneously. Results were promising enough for the design of a Phase I/IIa human study testing three doses of plasmin in MCA stroke within 8.5 hours of symptom onset.

Defibrinogenating Agents

The serine protease, ancrod, is derived from Malayan pit viper venom and produces a rapid reduction of fibrinogen when delivered intravenously. Dating back to the 1990s, human clinical trials suggested a clinical benefit, especially when patients were treated within 3 hours of symptom onset.[40, 41] However, despite rapid deribrinogenation, more recent large randomized clinical trials failed to show an improvement on clinical outcomes.[42, 43] It is hypothesized that failure to show improved outcomes in the recent studies may have resulted to relatively delayed time to treatment (~ 5 hours from symptom onset). Nevertheless, defibrinogention with medications like ancrod might still hold future promise in more carefully selected patients.

Endovascular Reperfusion Strategies

Current status of endovascular procedures to recanalize the vessels and reperfuse the brain reflects the dynamic nature of technology availability, development, and the need for evidence based practices. The first challenge is to train more neuro-endovascular specialists enough to provide 24x7x365 coverage at comprehensive stroke centers.[44] As time is brain, so is the success of an endovascular procedure: the longer the duration, the worse the outcomes.[45] Therefore, the second challenge is to develop technologies that can reach brain vessels at ease, be deployed fast with guaranteed probability of revascularization success. The progress of devices shows this trend (from Merci™, to Penumbra™, to now stent-assisted reperfusion): 56%, 83%, and 100% respectively.[46] In addition, alternative approaches are being explored combining tPA delivery with ultrasound (such as EKOS™ catheter used in the IMS-3 trial and microbubble infusion into the clot exposed to externally applied ultrasound).[47] Finally, it is mandatory to test our ability to open vessels with catheters in a randomized trial against current standard of care. This is a challenging task given the average time spent of these devices on the market and rapid emergence of novel and promisingly more potent technologies. Perhaps, such a trial should have adaptive design and test endovascular “kitchen sink” approach rather than a particular device.

IMS-3 should provide an answer whether bridging IV-IA approach is any better than standard IV-tPA treatment alone. However, we need to make a further step and find out if the primary IA approach is better than current medical therapy (both within and outside tPA window). Perhaps, technologies like stentrievers will be ready for the “prime-time” pivotal clinical trial.

Other Novel Experimental Approaches

End-diastolic flow augmentation

Since the degree of arterial recanalization and tissue reperfusion could be discrepant, we recently showed that the end-diastolic velocity (EDV) is more representative of tissue reperfusion than peak systoli and that a modest (10 cm/second) EDV increase during reperfusion therapy predicts early complete recanalization and subsequent neurological recovery.[48] End-diastolic flow augmentation thus could represent a novel target for enhancement of systemic therapies and for non-invasive alternative methods of brain perfusion augmentation. The latter is being studied in the NINDS-sponsored CUFFS trial that evaluates tolerability and dose escalation of the external counterpulsation (ECP) devices in ischemic stroke patients within 24 hours of symptom onset. ECP application produces a significant augmentation of the diastolic flow velocity[49], common carotid flow volume increase and a trend to greater reduction of the severity of the neurological deficit.[50]

Non-invasive Ventilatory Support

Blood flow occurs due to pressure gradients, and the presence of a proximal arterial occlusion causes distal arteriolar dilatation to maximum capacities in order to maintain tissue viability. Further vasodilatory stimuli can result in a decreasing in collateral flow to ischemic areas. We were able to document this steal in acute stroke patients in real time and link it to early neurological worsening and stroke recurrence.[51, 52] Termed the reversed Robin Hood (for analogy to “rob the poor to feed the rich”), this syndrome represents a link between sleep disordered breathing and worse stroke outcomes likely through hypoventilation and carbon dioxide retention.[53] It appears that this steal can be minimized by application of bi-level non-invasive ventilatory correction (Bi-PAP) that had good tolerability in a pilot study when Bi-PAP was deployed in the first hours post admission in patients with excessive sleepiness and persistent arterial occlusions without a formal sleep study.[54] The ability of this technology to augment brain perfusion and change natural history of stroke progression and recurrence should be tested in a clinical trial.

Sphenopalatine Ganglion Stimulation for Cerebral Blood Flow Augmentation

Animal models of ischemic stroke have demonstrated that electrical stimulation of the sphenopalatine ganglion (SPG) results in markedly increased in cerebral blood flow due to arterial vasodilation.[55] In humans, a 1-inch long implant is inserted using local anesthesia at the bedside through the greater palatine canal using a minimally invasive oral procedure. An external transmitter delivers the signal for stimulation of the SPG. A multicenter, international efficacy trial is currently ongoing which is randomizing 480 stroke patients out to 24-hours from symptom onset to either SPG stimulation or sham control.[56]

Conclusion

As cerebrovascular acute reperfusion strategies continue to develop beyond intravenous tPA, two distinct pathways are developing: invasive (i.e., endovascular) versus non-invasive (medical or mechanical adjunctive). Although the two modalities might appear conflicting, we argue that their development should occur simultaneously. The majority of IV-tPA delivery occurs in primary stroke centers where access to invasive modalities remains hours away from catheter insertion. Therefore, the future of reperfusion therapy likely begins with non-invasive strategies to maximize tPA-induced reperfusion and, if necessary, finishes with endovascular treatments that maximize high-rates of recanalization.

Acknowledgments

Acknowledgments:

None

Sources of Funding

Dr. Andrew D. Barreto is currently receiving NIH funding for the Argatroban TPA Stroke Study and Dr Andrei Alexandrov serves as Co-Investigator on CLOTBUST-HF project of the University of Texas-Houston Medical School Stroke Program (NINDS grant P50NS044227). Dr Barreto's work was also supported by the Center for Clinical and Translational Sciences, which is funded by NIH Clinical and Translational Award UL1 RR024148 [TL1 RR024147 for the T32 program; KL2 RR0224149 for the K12 program] from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the NIH.

References

1. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator. A science advisory from the american heart association/american stroke association. Stroke. 2009; 40:2945–2948. [PubMed: 19478221]
2. Lindsay P, Bayley M, McDonald A, Graham ID, Warner G, Phillips S. Toward a more effective approach to stroke: Canadian best practice recommendations for stroke care. CMAJ. 2008; 178:1418–1425. [PubMed: 18490636]
3. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol. 1992; 32:78–86. [PubMed: 1642475]
4. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, et al. Site of arterial occlusion identified by transcranial doppler predicts the response to intravenous thrombolysis for stroke. Stroke. 2007; 38:948–954. [PubMed: 17290031]
5. Jang IK, Brown DF, Giugliano RP, Anderson HV, Losordo D, Nicolau JC, et al. A multicenter, randomized study of argatroban versus heparin as adjunct to tissue plasminogen activator (tPA) in acute myocardial infarction: Myocardial infarction with novastan and tpa (MINT) study. J Am Coll Cardiol. 1999; 33:1879–1885. [PubMed: 10362188]
6. Kawai H, Umemura K, Nakashima M. Effect of argatroban on microthrombi formation and brain damage in the rat middle cerebral artery thrombosis model. Jpn J Pharmacol. 1995; 69:143–148. [PubMed: 8569051]
7. Jang IK, Gold HK, Leinbach RC, Fallon JT, Collen D. In vivo thrombin inhibition enhances and sustains arterial recanalization with recombinant tissue-type plasminogen activator. Circ Res. 1990; 67:1552–1561. [PubMed: 2123135]
8. Morris DC, Zhang L, Zhang ZG, Lu M, Berens KL, Brown PM, et al. Extension of the therapeutic window for recombinant tissue plasminogen activator with argatroban in a rat model of embolic stroke. Stroke. 2001; 32:2635–2640. [PubMed: 11692028]
9. LaMonte MP, Nash ML, Wang DZ, Woolfenden AR, Schultz J, Hursting MJ, et al. Argatroban anticoagulation in patients with acute ischemic stroke (ARGIS-1): A randomized, placebo-controlled safety study. Stroke. 2004; 35:1677–1682. [PubMed: 15155959]
10. Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, et al. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med. 2004; 351:2170–2178. [PubMed: 15548777]
11. Sugg RM, Pary JK, Uchino K, Baraniuk S, Shaltoni HM, Gonzales NR, et al. Argatroban tPA stroke study: Study design and results in the first treated cohort. Arch Neurol. 2006; 63:1057–1062. [PubMed: 16908730]
12. Mikulik R, Dufek M, Goldemund D, Reif M. A pilot study on systemic thrombolysis followed by low molecular weight heparin in ischemic stroke. Eur J Neurol. 2006; 13:1106–1111. [PubMed: 16987163]

13. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation. 2004; 110:588–636. [PubMed: 15289388]
14. Basinski A, Naylor CD. Aspirin and fibrinolysis in acute myocardial infarction: Meta-analytic evidence for synergy. J Clin Epidemiol. 1991; 44:1085–1096. [PubMed: 1834805]
15. Zinkstok SM, Vermeulen M, Stam J, de Haan RJ, Roos YB. Antiplatelet therapy in combination with rt-pa thrombolysis in ischemic stroke (ARTIS): Rationale and design of a randomized controlled trial. Cerebrovasc Dis. 2010; 29:79–81. [PubMed: 19907167]
16. Zinkstok SM, Vermeulen M, Stam J, de Haan RJ, Roos YB. A randomised controlled trial of antiplatelet therapy in combination with rt-pa thrombolysis in ischemic stroke: Rationale and design of the ARTIS-trial. Trials. 2010; 11:51. [PubMed: 20459856]
17. Ohman EM, Kleiman NS, Gacioch G, Worley SJ, Navetta FI, Talley JD, et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. IMPACT-AMI investigators. Circulation. 1997; 95:846–854. [PubMed: 9054741]
18. Topol EJ. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: The GUSTO V randomised trial. Lancet. 2001; 357:1905–1914. [PubMed: 11425410]
19. Siebler, M. Safety of tirofiban in acute ischemic stroke (abstract). European Stroke Conference; 2006.
20. Adams HP Jr, Effron MB, Torner J, Davalos A, Frayne J, Teal P, et al. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: Results of an international phase III trial: Abciximab in emergency treatment of stroke trial (ABESTT-II). Stroke. 2008; 39:87–99. [PubMed: 18032739]
21. Torgano G, Zecca B, Monzani V, Maestroni A, Rossi P, Cazzaniga M, et al. Effect of intravenous tirofiban and aspirin in reducing short-term and long-term neurologic deficit in patients with ischemic stroke: A double-blind randomized trial. Cerebrovasc Dis. 2010; 29:275–281. [PubMed: 20090319]
22. Mousa SA. In-vitro efficacy of different platelet glycoprotein IIb/IIIa antagonists and thrombolytics on platelet/fibrin-mediated clot dynamics in human whole blood using thrombelastography. Blood Coagul Fibrinolysis. 2007; 18:55–60. [PubMed: 17179828]
23. Nakada MT, Montgomery MO, Nedelman MA, Guerrero JL, Cohen SA, Barnathan ES, et al. Clot lysis in a primate model of peripheral arterial occlusive disease with use of systemic or intraarterial reteplase: Addition of abciximab results in improved vessel reperfusion. J Vasc Interv Radiol. 2004; 15:169–176. [PubMed: 14963184]
24. Pancioli AM, Broderick J, Brott T, Tomsick T, Khoury J, Bean J, et al. The combined approach to lysis utilizing eptifibatide and rt-PA in acute ischemic stroke: The CLEAR stroke trial. Stroke. 2008; 39:3268–3276. [PubMed: 18772447]
25. University of Cincinnati. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Study of the combination therapy of rt-PA and eptifibatide to treat acute ischemic stroke (CLEAR-ER). [cited 2011 Feb 22]. Available from: http://clinicaltrials.gov/show/NCT00894803 NLM Identifier: NCT00894803
26. Warach, S. International stroke conference -late breaking abstracts. February. 2006 Reopro retavase reperfusion of stroke safety study -imaging evaluation.
27. Daffertshofer M, Gass A, Ringleb P, Sitzer M, Sliwka U, Els T, et al. Transcranial low-frequency ultrasound-mediated thrombolysis in brain ischemia: Increased risk of hemorrhage with combined ultrasound and tissue plasminogen activator: Results of a phase II clinical trial. Stroke. 2005; 36:1441–1446. [PubMed: 15947262]
28. Molina CA, Ribo M, Rubiera M, Montaner J, Santamarina E, Delgado-Mederos R, et al. Microbubble administration accelerates clot lysis during continuous 2-MHz ultrasound monitoring in stroke patients treated with intravenous tissue plasminogen activator. Stroke. 2006; 37:425–429. [PubMed: 16373632]

29. Molina CA, Barreto AD, Tsivgoulis G, Sierzenski P, Malkoff MD, Rubiera M, et al. Transcranial ultrasound in clinical sonothrombolysis (TUCSON) trial. Ann Neurol. 2009; 66:28–38. [PubMed: 19670432]
30. Tsivgoulis G, Eggers J, Ribo M, Perren F, Saqqur M, Rubiera M, et al. Safety and efficacy of ultrasound-enhanced thrombolysis: A comprehensive review and meta-analysis of randomized and nonrandomized studies. Stroke. 2010; 41:280–287. [PubMed: 20044531]
31. The University of Texas Health Science Center, Houston. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Combined lysis of thrombus in brain ischemia with transcranial ultrasound and systemic t-PA- hands-free. A phase I/II pilot safety trial. [cited 2011 Feb 22]. Available from: http://clinicaltrials.gov/show/NCT01240356 NLM Identifier: NCT01240356
32. Cerevast Therapeutics. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. A randomized, active controlled, double-blinded trial of the combined lysis of thrombus with ultrasound and systemic tissue plasminogen activator (tPA) for emergent revascularization (CLOTBUSTER) in acute ischemic stroke. [cited 2011 Sept 22]. Available from: http://clinicaltrials.gov/show/NCT01098981 NLM Identifier: NCT01098981
33. Thomas GR, Thibodeaux H, Errett CJ, Badillo JM, Keyt BA, Refino CJ, et al. A long-half-life and fibrin-specific form of tissue plasminogen activator in rabbit models of embolic stroke and peripheral bleeding. Stroke. 1994; 25:2072–2078. [PubMed: 8091454]
34. Haley EC Jr, Lyden PD, Johnston KC, Hemmen TM. A pilot dose-escalation safety study of tenecteplase in acute ischemic stroke. Stroke. 2005; 36:607–612. [PubMed: 15692126]
35. Haley EC Jr, Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, et al. Phase IIb/III trial of tenecteplase in acute ischemic stroke: Results of a prematurely terminated randomized clinical trial. Stroke. 2010; 41:707–711. [PubMed: 20185783]
36. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, et al. The desmoteplase in acute ischemic stroke trial (DIAS): A phase II mri-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke. 2005; 36:66–73. [PubMed: 15569863]
37. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, et al. Dose escalation of desmoteplase for acute ischemic stroke (DEDAS): Evidence of safety and efficacy 3 to 9 hours after stroke onset. Stroke. 2006; 37:1227–1231. [PubMed: 16574922]
38. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): A prospective, randomised, double-blind, placebo-controlled study. Lancet Neurol. 2009; 8:141–150. [PubMed: 19097942]
39. Marder VJ, Jahan R, Gruber T, Goyal A, Arora V. Thrombolysis with plasmin: Implications for stroke treatment. Stroke. 2010; 41:S45–49. [PubMed: 20876504]
40. The ancrod stroke study investigators. Ancrod for the treatment of acute ischemic brain infarction. Stroke. 1994; 25:1755–1759. [PubMed: 8073455]
41. Sherman DG, Atkinson RP, Chippendale T, Levin KA, Ng K, Futrell N, et al. Intravenous ancrod for treatment of acute ischemic stroke: The STAT study: A randomized controlled trial. Stroke treatment with ancrod trial. JAMA : the journal of the American Medical Association. 2000; 283:2395–2403. [PubMed: 10815082]
42. Levy DE, del Zoppo GJ, Demaerschalk BM, Demchuk AM, Diener HC, Howard G, et al. Ancrod in acute ischemic stroke: Results of 500 subjects beginning treatment within 6 hours of stroke onset in the ancrod stroke program. Stroke. 2009; 40:3796–3803. [PubMed: 19875736]
43. Hennerici MG, Kay R, Bogousslavsky J, Lenzi GL, Verstraete M, Orgogozo JM. Intravenous ancrod for acute ischaemic stroke in the european stroke treatment with ancrod trial: A randomised controlled trial. Lancet. 2006; 368:1871–1878. [PubMed: 17126719]
44. Leifer D, Bravata DM, Connors JJ 3rd, Hinchey JA, Jauch EC, Johnston SC, et al. Metrics for measuring quality of care in comprehensive stroke centers: Detailed follow-up to brain attack coalition comprehensive stroke center recommendations: A statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2011; 42:849–877. [PubMed: 21233469]

45. Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology. 2009; 73:1066–1072. [PubMed: 19786699]
46. Levy EI, Siddiqui AH, Crumlish A, Snyder KV, Hauck EF, Fiorella DJ, et al. First food and drug administration-approved prospective trial of primary intracranial stenting for acute stroke: SARIS (stent-assisted recanalization in acute ischemic stroke). Stroke. 2009; 40:3552–3556. [PubMed: 19696415]
47. Ribo M, Molina CA, Alvarez B, Rubiera M, Alvarez-Sabin J, Matas M. Intra-arterial administration of microbubbles and continuous 2-MHz ultrasound insonation to enhance intra-arterial thrombolysis. J Neuroimaging. 2010; 20:224–227. [PubMed: 19226340]
48. Alexandrov AV, Tsivgoulis G, Rubiera M, Vadikolias K, Stamboulis E, Molina CA, et al. End-diastolic velocity increase predicts recanalization and neurological improvement in patients with ischemic stroke with proximal arterial occlusions receiving reperfusion therapies. Stroke. 2010; 41:948–952. [PubMed: 20224054]
49. Alexandrov AW, Ribo M, Wong KS, Sugg RM, Garami Z, Jesurum JT, et al. Perfusion augmentation in acute stroke using mechanical counter-pulsation-phase IIa: Effect of external counterpulsation on middle cerebral artery mean flow velocity in five healthy subjects. Stroke. 2008; 39:2760–2764. [PubMed: 18658038]
50. Han JH, Leung TW, Lam WW, Soo YO, Alexandrov AW, Mok V, et al. Preliminary findings of external counterpulsation for ischemic stroke patient with large artery occlusive disease. Stroke. 2008; 39:1340–1343. [PubMed: 18309160]
51. Alexandrov AV, Nguyen HT, Rubiera M, Alexandrov AW, Zhao L, Heliopoulos I, et al. Prevalence and risk factors associated with reversed robin hood syndrome in acute ischemic stroke. Stroke. 2009; 40:2738–2742. [PubMed: 19461025]
52. Palazzo P, Balucani C, Barlinn K, Tsivgoulis G, Zhang Y, Zhao L, et al. Association of reversed robin hood syndrome with risk of stroke recurrence. Neurology. 2010; 75:2003–2008. [PubMed: 21115955]
53. Barlinn K, Alexandrov AV. Sleep-disordered breathing and arterial blood flow steal represent linked therapeutic targets in cerebral ischaemia. Int J Stroke. 2011; 6:40–41. [PubMed: 21205239]
54. Tsivgoulis G, Zhang Y, Alexandrov AW, Harrigan MR, Sisson A, Zhao L, et al. Safety and tolerability of early noninvasive ventilatory correction using bilevel positive airway pressure in acute ischemic stroke. Stroke. 2011; 42:1030–1034. [PubMed: 21372308]
55. Toda N, Tanaka T, Ayajiki K, Okamura T. Cerebral vasodilatation induced by stimulation of the pterygopalatine ganglion and greater petrosal nerve in anesthetized monkeys. Neuroscience. 2000; 96:393–398. [PubMed: 10683579]
56. BrainsGate. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Implant for augmentation of cerebral blood flow trial, effectiveness and safety in a 24 hour window (impact-24). [cited 2011 Sept 22]. Available from: http://clinicaltrials.gov/show/NCT00826059 NLM Identifier: NCT00826059

Table

Summary of adjunctive and alternative approaches to reperfusion therapy in acute ischemic stroke.

Category	Agent or Device	Description	Current phase of testing
Combinatory approaches	**1** tPA + direct thrombin inhibition **2** tPA + low molecular weight heparin **3** tPA + acetylsalicylic acid **4** fibrinolytic (tPA or reteplase) + GPIIb/IIIa inhibitors **5** Sonothrombolysis (tPA + therapeutic ultrasound)	Agents combined to enhance the efficacy of fibrinolytics, prevent arterial re-occlusion and/or improve microcirculatory flow.	**1** II **2** None current **3** III **4** II **5** II & III
Novel Systemic Thrombolytic or Defibrinogenating agents	**1** Tenecteplase (TNK) **2** Desmoteplase **3** Plasmin **4** Ancrod	Agents tested in either: • an extended time window from symptom onset (i.e., >4.5 hours) • head-to-head comparison with intravenous tPA	**1** None, recently completed Phase II **2** Phase III **3** I/IIa **4** None current
Endovascular medical or mechanical reperfusion treatments	**1** Interventional Management of Stroke-3 (IMS-3) **2** MR and Recanalization of Stroke Clots Using Embolectomy(MR RESCUE)	Direct intra-arterial approach allows for local lytic application and greater rates of arterial recanalization.	**1** III **2** II
Non-invasive or minimally-invasive methods to augment cerebral blood flow and alleviate intracranial blood flow steal	**1** External counterpulsation **2** Non-invasive ventilatory support in stroke patients with steal **3** Sphenopalatine ganglion (SPG) stimulation **4** Partial aortic occlusion	**1** Device applies one hour of full-pressure (or sham) external cuff inflation around the lower extremities timed with the patient's electrocardiogram. **2** Application of bi-level ventilation improves intracranial steal in documented arterial occlusion. **3** Stimulation of SPG increases cerebral blood flow. **4** Abdominal intra-aortic catheter partially obstructs blood flow increases cerebral blood flow.	**1** I **2** None current **3** III **4** None, recently completed Phase III