

Thrombolysis For Ischemic Stroke, Where We Are.

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Citation

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Abstract

For years, the management of acute ischemic stroke has been a source of frustration and dismay for physicians, families, and even patients alike, as effective treatment to reverse a neurologic deficit was lacking. The application of fibrinolysis has revolutionized the care for patients with acute ischemic stroke in the clinical practice. Intravenous recombinant tissue plasminogen activator (rt-PA) has been proven to improve functional outcomes following acute ischemic stroke and can be administered to a select group of patients up to 4.5 h after symptom onset. ``Time is brain`` ; Time from symptom onset to thrombolysis is the most important determinant of the success of treatment, with greatest efficacy if given within 90 min. Hospitals should implement standardized processes and protocols for acute stroke to guide immediate patient assessment, brain imaging, drug administration, and post-thrombolysis care. In the other hand ``Physiology is brain``, is new replacing concept as imaging technology can potentially free us from the time constrains by objectively demarcating the penumbra regardless of the time frame and therefore unleashing this hidden dimension that can help expand the benefit of thrombolysis to a wider acute stroke patients population (Mansour et al., 2010).

INTRODUCTION

In this article we review the clinical application of thrombolysis, care of acute stroke patients, current evidence regarding fibrinolysis, and future direction of penumbral imaging to determine candidates for recanalization therapies.

The concept of pharmacological fibrinolysis for the treatment of acute ischemic stroke developed from the finding that early reperfusion improved outcomes in various experimental animal models of intracranial vessel occlusion and the recognition that the mechanisms for endogenous fibrinolysis in humans are often insufficient to prevent brain infarction in many patients (Meschia et al., 2002). The clinical application of fibrinolysis revolutionized ischemic stroke care by offering an effective treatment for a disease in which previously all medical efforts were restricted to preventing the recurrent events, avoidance of secondary complications, and rehabilitation.

MECHANISMS OF FIBRINOLYSIS

the story start when a clot is formed where a plasminogen gets trapped within it. The injured tissues and vascular endothelium then slowly release tissue plasminogen activator (t-PA) which in turn converts plasminogen to plasmin. Plasmin (a plasma protein) is a potent proteolytic enzyme that digests fibrin (the main protein component of

the clot) into fibrin degradation products. This process ensures the clot dissolution and protects blood flow, particularly in the microcirculation.

FIBRINOLYSIS FOR THE TREATMENT OF ISCHEMIC STROKE

THE EVIDENCE

The pivotal trial leading to the international approval of intravenous rt-PA for the treatment of cerebral ischemia was the NINDS rt-PA Stroke Study (NINDS rt-PA Stroke Study Group , 1995). In this trial, 624 patients were randomized to receive intravenous rt-PA (0.9 mg/kg, maximum 90 mg) or placebo within 3 h of stroke symptom onset. Treatment with intravenous rt-PA was associated with at least 30% increase in the chances of achieving functional independence with complete or nearly complete neurological recovery at 3 months (NINDS rt-PA Stroke Study Group , 1995). The main risk of treatment was symptomatic intracerebral hemorrhage, which occurred in 6.4% of patients treated with rt-PA versus 0.6% of patients who received placebo, but it did not result in an increase in mortality among rt-PA-treated patients. Efficacy was greatest for patients treated within 90 min of symptom onset. For patients treated within 90 min the odds ratio for complete recovery was 2.11 compared with an odds ratio of 1.69 for patients treated within 91–180 min (Marler et al., 2000). Functional benefit was sustained at

1 year (Kwiatkowski et al., 1999). Subgroup analyses confirmed that the efficacy of intravenous rt-PA extended to all patients meeting the trial inclusion and exclusion criteria, including older patients with severe strokes at presentation (NINDS rt-PA Stroke Study Group, 1995).

Shortly after publication of the NINDS trial, rt-PA was approved for intravenous use in patients with acute ischemic stroke in the USA mostly following the patient selection criteria of NINDS study.

Later on, additional radiological exclusion criteria was added based on the finding that the presence of large early ischemic changes on baseline CT scan was associated with higher risk of symptomatic intracranial hemorrhage and results from earlier European studies that suggested poorer outcomes in patients with multilobar low attenuation changes (von Kummer and Hacke, 1992) which had led to the exclusion of these patients from subsequent European trials. Since then, treatment with intravenous rt-PA has gained acceptance across the globe and its effectiveness has been confirmed in multiple post-marketing observational studies.

Early intravenous administration of recombinant tissue plasminogen activator (rt-PA, Alteplase) has been proven to improve functional outcome after acute ischemic stroke (Adams et al., 2007).

A large observational study has the SITS-MOST (Wahlgren et al., 2007), which enrolled nearly 6,500 patients from 14 European countries. Intravenous fibrinolysis with rt-PA was at least as safe and effective in routine clinical practice as it had been in the randomized trials (Wahlgren et al., 2007; Wahlgren et al., 2008b). Over three-quarters of treated patients had moderate to severe strokes at baseline and 55% were independent at 3 months despite only 10.6% being treated within 90 min (versus half of the rt-PA group in the NINDS trial). Even centers with limited experience on the administration of fibrinolysis for acute stroke achieved good results when adhering to the accepted indications and contraindications. The risk of intracranial hemorrhage, defined using various criteria, was acceptably low. Additionally, Substantial neurological decline from brain hemorrhage only occurred in 1.7% of patients.

Now, despite the availability of thrombolytic therapy that leads to better outcomes, the exasperation continues as the percentage of patients receiving such treatment languishes in the single digits. The main reason for the limited application of this effective intervention in clinical practice is that

patients often arrive to the Emergency Department too late. As a consequence, there has been a lot of interest in extending the therapeutic window for acute reperfusion therapies, including intravenous rt-PA.

A pooled analysis of six major trials evaluating the effectiveness of intravenous rt-PA for acute ischemic stroke within up to 6 h from symptom onset suggested that fibrinolysis could produce clinical benefit when administered beyond 3 h (Hacke et al., 2004). In fact, this analysis showed that the benefit was much greater over the first 90 min from symptom onset, but much more similar when time to treatment was 91–180 and 181–270 min. These findings were the motive for the design of the ECASS III trial, a multi-center, randomized trial conducted in Europe to evaluate intravenous rt-PA versus placebo administered between 3 and 4.5 h after onset of ischemic stroke symptoms (Hacke et al., 2008) where a total of 821 patients were enrolled, nearly one-third more than in the NINDS trial. Treatment with rt-PA was associated with a significant improvement in the rate of favorable functional outcome using various scales. Overall, the chances to regain full independence were 28% higher among patients treated with rt-PA and 14 patients had to be treated for one additional patient to achieve a favorable outcome. Mortality was not significantly different between the groups, but slightly higher in the placebo arm. The rate of symptomatic intracranial hemorrhage as defined by the NINDS criteria was 7.9% in the rt-PA group (versus 6.4% in the NINDS trial), but only 2.4% of them were considered to have worsened because of the bleeding. A subsequent analysis confirmed the efficacy of rt-PA in various subgroups treated within the 3–4.5 h window, including patients of older age and across all severities of stroke (Bluhmki et al., 2009). Intravenous fibrinolysis with rt-PA within 3 and 4.5 h was also shown to be safe in large European observational study (SITS-ISTR) which included over 650 patients treated in that time window (Wahlgren et al., 2008a). Therefore, intravenous rt-PA should be considered for selected patients with symptom duration between 3 and 4.5 h. It should be noted that there are additional exclusion criteria for the 3–4.5 h time window, as patients with certain characteristics were not studied. These include very severe deficits at onset (NIHSS >25), octogenarian population, combination of history of previous stroke and diabetes mellitus, and oral anticoagulation regardless of INR at presentation.

PATIENT SELECTION

Acute stroke patients must be evaluated emergently for

consideration of recanalization treatments. Each hospital needs to implement a stroke code process to streamline immediate patient assessment, brain imaging, and drug administration. Development of critical care pathways (ideally starting from assessment in the field by paramedics or other first responders), easily accessible written protocols, and order sets is highly useful to ensure rapid and effective evaluation and treatment. Hospitals should monitor their performance to recognize areas for improvement and to ensure consistent compliance with the recommended time metrics (Table 1).

Figure 1

Table 1. Time needed from acute stroke presentation to fibrinolytic treatment.

Step of care	Target time
Evaluation by physician	10 min
Brain imaging	25 min
Interpretation of brain imaging (door-to-interpretation)	45 min
Start of fibrinolysis (door-to-needle)	60 min

Strict adherence to the prescribed criteria for patient selection is mandatory to avoid complications and optimize the likelihood of benefit from IF. The indications and contraindications for treatment with intravenous rt-PA are summarized in Table 2. Notice that some additional contraindications should be respected when contemplating the use of rt-PA between 3 and 4.5 h. Treatment in patients without a suspected coagulopathy (e.g., no recent or current administration of anticoagulants, no history of thrombocytopenia, end-stage liver disease or hematologic disorder) should not be delayed for laboratories with long turnaround times. However, thrombolysis can be safely administered in these patients before the results of clotting tests are available (Rost et al., 2009). Ischemic stroke mimickers (e.g., migraine, seizure, or conversion disorder) should be kept in mind, but fear of misdiagnosis should not prevent initiation of intravenous thrombolysis if the clinician has reasonable concern for acute ischemic stroke. A recent retrospective study found zero instances of intracranial hemorrhage in patients with stroke mimics (Chernyshev et al., 2010).

Figure 2

Table 2. Indications and contraindications for IV- rt-PA in acute ischemic stroke.

Indications
Diagnosis of ischemic stroke causing a measurable neurological deficit
Onset of symptoms <4.5 h before initiation of treatment
CONTRAINDICATIONS
Clinical
Sustained hypertension above 180/110 mm Hg
Symptoms suggestive of subarachnoid hemorrhage
Previous history of intracranial hemorrhage
ST elevation myocardial infarction within the previous 3 months
Major head trauma or stroke within the previous 3 months
Major surgery within the previous 14 days
Gastrointestinal or urinary tract hemorrhage within the previous 21 days
Arterial puncture at a non-compressible site within the previous 7 days
Active bleeding or acute traumatic fracture on examination
Seizure at onset with suspected postictal deficits
Minor or rapidly improving neurological deficits
Radiological
Head CT showing hemorrhage or multilobar infarction (i.e., hypodensity involving >1/3 of the cerebral hemisphere)
Laboratory
Oral anticoagulation with INR >1.7*
Heparin within previous 48 h with elevated current aPTT
Platelet count <100,000 per mm ³
Blood glucose level <50 mg/dL (2.7 mmol/L) at presentation with improving deficits following correction of hypoglycemia
Additional contraindications for treatment between 3 and 4.5 h
Age >80 years
Very severe deficits at onset (NIHSS score >25)
Combination of previous stroke and diabetes mellitus

*Oral anticoagulation regardless of current INR should be considered a contraindication for treatment between 3 and 4.5 h.

Current guidelines on rt-PA administration are based on the definition of symptom onset as the last time that the patient was symptom-free or at his/her previous baseline (Adams et al., 2007). For patients who wake up stroke, the time of onset is considered the last time the patient was awake and without the symptoms. A recent transient ischemic attack similar to the current symptoms is generally not considered a contraindication for fibrinolysis; the clock can be reset to the time of onset of the new symptoms as long as there is clear knowledge that the previous symptoms resolved fully.

Some factors initially listed among the exclusion criteria for IVF in the seminal trials are no longer considered to be contraindications in practice. For instance, the report of a seizure at the onset of deficits should not preclude fibrinolysis as long as the treating physician realized that the persistent deficits are secondary to a stroke and not merely a postictal phenomenon (Adams et al., 2007). A similar

reasoning might applied to hypoglycemic patients who fail to improve after administration of dextrose. One should also be careful when deciding not to treat a stroke patient with fibrinolysis because of mild or rapidly improving symptoms. All too often, these patients subsequently suffer permanent drastic disability from those strokes (Barber et al., 2001).

Interpretation of brain imaging in the emergency setting has the primary objective of excluding intracranial hemorrhage. Non-contrast CT scan of the head is sufficient for this goal and emergency treatment should not be delayed in order to obtain more advanced imaging modalities (such as multimodality MRI and multimodality CT) (Adams et al., 2007).

However, Imaging holds the key for further development despite some limitations. Perfusion/diffusion mismatch can provide a working estimate of the ischemic penumbra in hyperacute stroke and has been successfully used to triage patients. We should keep in mind that Physiology is brain can expand the therapeutic window for thrombolytic therapy.

Apart from hemorrhage, only the presence of multilobar hypodensity (involving more than 1/3 of the cerebral hemisphere) should be considered a radiological contraindication for fibrinolysis (Figure 1). Other CT findings may have prognostic value but they do not negate the benefit of fibrinolysis and should not preclude its use (Figure 2). For instance, the presence of a hyperdense middle cerebral artery sign is associated with worse prognosis (Qureshi et al., 2006) and higher risk of hemorrhage after fibrinolysis (Derex et al., 2005), but intravenous rt-PA can still be useful for these patients (Qureshi et al., 2006). Other early signs of brain ischemia can often be seen when the CT scan is assessed in detail, such as loss of insular ribbon, obscuration of the lenticular nucleus, loss of gray–white matter differentiation, and sulcal effacement. However, these signs do not have the same implication as areas of definite hypodensity because they probably indicate focal tissue edema rather than established infarction (Muir et al., 2006).

Figure 3

Figure 1. CT scan of the head without contrast showing multilobar hypodensity in the left hemisphere (arrows).

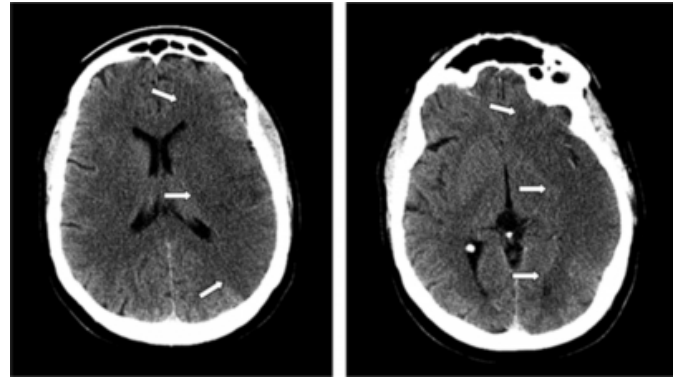
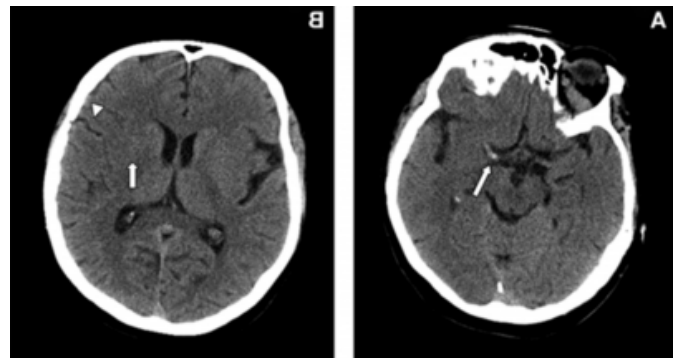


Figure 4

Figure 2. (A) Axial non-contrast CT of the head demonstrates a right hyperdense middle cerebral artery sign indicative of acute thrombus (arrow). (B) CT scan of the head without contrast showing effacement of sulci and Sylvian fissure (arrowhead) and loss of distinction of the margins of the right lenticular nucleus (arrow).



Adequate control of blood pressure along all process of administration of intravenous fibrinolysis must be achieved to reduce the risk of intracranial bleeding (Table 3).

Figure 5

Table 3. Blood Pressure Management in patients with acute ischemic stroke who are candidates for fibrinolysis.

Before fibrinolysis

If SBP >185 mm Hg or DBP >110 mm Hg
Labetalol 10–20 mg IV over 1–2 min (may repeat once)
or
Nicardipine infusion at 5–15 mg/h

If BP controlled, administer fibrinolysis
If BP still >185/110 mm Hg, do NOT proceed with fibrinolysis

After fibrinolysis

If SBP 180–230 mm Hg or DBP 105–120 mm Hg
Labetalol 10–20 mg IV over 1–2 min,
may repeat every 10–20 min up to 300 mg over 24 h
or
Labetalol 10–20 mg IV followed by infusion at 2–8 mg/min
or
Nicardipine infusion at 5–15 mg/h

If SBP >230 mm Hg or DBP >120 mm Hg
Sodium nitroprusside infusion at 0.5–3 mcg/kg/min (doses of up to 10 mcg/kg/min can be safely administered for up to 10 min)

*This protocol also applies to other forms of reperfusion therapy apart from intravenous rt-PA.
BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.*

FIBRINOLYSIS AND POST-FIBRINOLYSIS CARE

Infusion of the fibrinolytic agent should be started in the Emergency Department without delay as soon as the patient is determined to be a good treatment candidate. After fibrinolysis, the patient should be admitted to a Stroke Unit for strict neurological monitoring by specialized nurses. Post-fibrinolytic management should be ideally guided by a written protocol to ensure optimal care and avoid risks. Patients should be kept on cardiac telemetry for at least the first 24 h.

Neurologic assessments and blood pressure measurements should be performed every 15 min during the infusion, followed by every 30 min for the first 6 h, and then hourly until 24 h after treatment. The rationale for such close blood pressure monitoring is that excessive hypertension in patients treated with intravenous rt-PA is associated with the development of symptomatic hemorrhagic transformation. Hypertension in the 24 h post-fibrinolysis is preferably treated with intravenous labetalol or nicardipine infusion. If systolic blood pressure exceeds 230 mm Hg or diastolic blood pressure exceeds 120 mm Hg, intravenous continuous infusions of antihypertensives (e.g., sodium nitroprusside) should be considered. If the patient develops severe headache, vomiting, or acute refractory hypertension (BP >180/110), an emergency head CT should be obtained to

exclude hemorrhage.

Bleeding complications in general and intracranial hemorrhage in particular are the most common and feared adverse events after intravenous fibrinolysis. However, disabling or fatal intracranial hemorrhages after fibrinolysis typically occur in older patients with severe deficits and large areas of ischemia at presentation (Albers et al., 2006; Saver, 2007). In other words, severe brain hemorrhages usually complicate fibrinolytic therapy in patients who already had very poor prognosis from presentation. Consequently, few patients are actually harmed by intravenous rt-PA (number needed to harm has been estimated to be 126 for disabled or fatal outcome and 36.5 for worsened outcome among patients treated within 3 h of symptom onset) (Saver, 2007).

Hyperglycemia and fever have been independently associated with increased risk of poor outcome in the setting of acute ischemic stroke. Any fever should be investigated for source as it may be the first sign of an infectious complication such as pneumonia. Strict monitoring of blood glucose (with insulin as needed to maintain levels between 140 and 180 mg/dL) and avoidance of hyperthermia are essential measures of supportive care. Follow-up brain imaging should be obtained at 24 h after treatment, prior to the initiation of antithrombotics (antiplatelet agents or anticoagulants).

Additional complications from rt-PA include angioedema, which may cause partial airway obstruction, and, very rarely, myocardial rupture in patients with previous large myocardial infarctions.

OUTCOME PREDICTORS OF AFTER IVF

The most important predictor is worse neurological deficits (i.e., higher NIHSS score) and disturbances of consciousness at presentation at presentation, higher admission blood glucose level, old age, and early ischemic changes and hyperdense middle cerebral artery sign on baseline CT scan are the main predictors of poor outcome upon initial evaluation (NINDS rt-PA Stroke Study Group, 1995; Bruno et al., 2002; Heuschmann et al., 2004; Qureshi et al., 2006; Wahlgren et al., 2008b; Mateen et al., 2009). Time to fibrinolysis administration has a strong inverse association with functional outcome across strokes of different severity (Marler et al., 2000; Hacke et al., 2004). Hyperglycemia and intracranial hemorrhage predict hyperacute clinical worsening after fibrinolysis (Leigh et al., 2004). Lack of improvement at 24 h predict worse outcome at 90 days

follow-up (Saposnik et al., 2004). Hyperglycemia, time to fibrinolytic therapy, and cortical involvement have been associated with lack of improvement during the first day (Saposnik et al., 2004). The detrimental effects of hyperglycemia may be at least partially explained by lower rates of recanalization, where could be related to a hyperglycemia-induced decrease in fibrinolytic activity (Ribo et al., 2005).

The main predictors of symptomatic intracranial hemorrhage are old age – although intravenous rt-PA can be administered to selected old patients ; with acceptable safety margin – (Sylaja et al., 2006; Mateen et al., 2010), higher initial NIHSS, larger area of ischemia, and higher blood glucose levels (Kidwell et al., 2002; Hacke et al., 2004; Albers et al., 2006). Longer time to fibrinolysis has been associated with higher risk of intracranial hemorrhage in some (Kidwell et al., 2002) but not all studies (Hacke et al., 2004). Higher systolic blood pressure may also increase the risk of intracranial hemorrhage (Wahlgren et al., 2008b), but especially when currently recommended parameters for blood pressure controlled are not respected. Other protocol violations, most notably the use of antithrombotic agents during the first 24 h, can markedly increase the risk of hemorrhage (Katzan et al., 2000).

SELECTION OF CANDIDATES FOR INTRAVENOUS FIBRINOLYSIS USING PENUMBRAL IMAGING

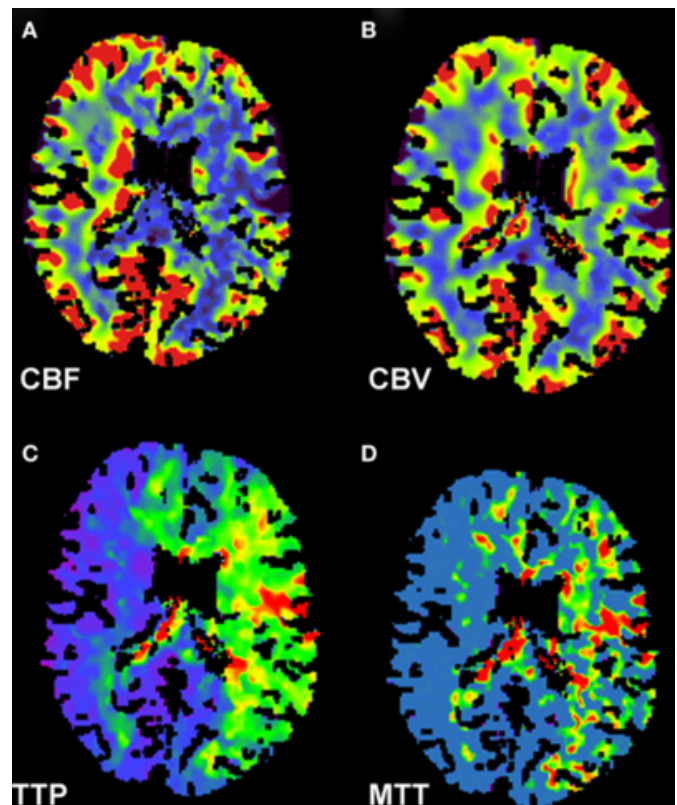
It was proposed to facilitate the selection of patients with a salvageable area as PWI/DWI mismatch is considered to represent the tissue that is not irreversibly injured and can respond to early reperfusion therapy. In order to clarify the clinical significance of PWI/DWI mismatch in the selection of candidates for tPA therapy, some multicenter trials were performed. Results of desmoteplase in acute ischemic stroke (DIAS), dose escalation of desmoteplase for acute ischemic stroke (DEDAS), DIAS-2 did not definitely demonstrate the clinical benefits of desmoteplase administration in patients with PWI/DWI mismatch between 3 and 9 h of onset; moreover, DIAS-2 could not prove any effect of the drug. However, many lacuna of the study were revealed that explain these shocking results and were considered enough rationale for the dawning of the DIAS-3 trial. Diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE), in which tPA was administered to all participants between 3 and 6 h of stroke onset, showed that the occurrence of early reperfusion led to a favorable clinical response in patients with PWI/DWI mismatch. In contrast,

early reperfusion was not beneficial in patients without PWI/DWI mismatch (Albers et al., 2006).

Proponents of this model argue that documentation of persistent ischemic penumbra (i.e., hypoperfused but salvageable tissue) should represent a solid indication for reperfusion treatments regardless of duration of symptoms. There is strong physiological rationale to support the concept that imaging of the ischemic penumbra with MRI diffusion-weighted (DWI) and perfusion-weighted (PWI) or CT perfusion (CTP) can extend the therapeutic window for reperfusion therapies, including fibrinolysis. A comparison of CTP sequences of mean transit time, cerebral blood flow, and cerebral volume may identify whether there is salvageable ischemic penumbra or if the infarct has been completed (Figure 3). Consequently, assuming that brain imaging can reliably recognize penumbral tissue and discriminate patients at excessive risk for bleeding in the infarct core, the concept should be valid. However, these assumptions remain to be proven.

Figure 6

Figure 3. CT perfusion scan of the head demonstrates findings consistent with large ischemic penumbra. Decreased cerebral blood flow (A), preserved cerebral blood volume (B), and prolonged time to peak (C) and mean transit time (D) in the left middle cerebral and bilateral anterior cerebral artery distributions are shown.



The randomized trial EPITHET assigned 101 patients to receive intravenous rt-PA or placebo 3–6 h after stroke onset (Davis et al., 2008). All patients were studied with MRI with DWI-PWI before and a few days after treatment, but the radiological findings did not affect treatment assignment. DWI-PWI was present in 86% of patients. Reperfusion occurred in 39% of mismatch patients and these patients had less infarct growth and better functional outcome (defined as modified Rankin score ≤ 2 at 90 days). The rate of symptomatic intracranial hemorrhage was quite low (4%) and the risk of this complication did not correlate with baseline volume of restricted diffusion. In addition to DWI-PWI mismatch, there has been some interest in whether a clinical-diffusion mismatch (CDM, the comparison of severity of clinical deficits measured by NIHSS and area of restricted diffusion on MRI) can select patients for thrombolytic therapy. This was not supported in a substudy of EPITHET, in which there was no increased benefit from rt-PA in patients with CDM (Ebinger et al., 2009).

A recent study compared intravenous tenecteplase administered between 3 and 6 h from symptom onset on patients with documented penumbra (defined by MRI with DWI-PWI or CTP) and vessel occlusion (defined by non-invasive angiogram) versus control patients treated with intravenous rt-PA within 3 h according to current guidelines (Parsons et al., 2009). Although the relatively small size of the study ($n = 50$, included only 15 treated with tenecteplase) and methodological limitations preclude definite conclusions, the high degrees of reperfusion (74%) and rates of recanalization (10/15 cases) among patients selected on the basis of penumbral imaging was promising. Pilot trials testing intravenous desmoteplase between 3 and 9 h from symptom onset in patients with DWI-PWI mismatch on baseline MRI had shown encouraging results (Hacke et al., 2005; Furlan et al., 2006). However, the larger DIAS-2 study did not confirm this benefit (Hacke et al., 2009). A preponderance of mild strokes with small core lesions and mismatch volumes may have limited the power of DIAS-2 to detect some therapeutic effect.

An ongoing trial (MR RESCUE) is assessing the value of endovascular reperfusion within 3–8 h of symptom onset among patients with DWI-PWI mismatch on MRI. At this point, we still do not have sufficient information to recommend the use of penumbral imaging to select patients for fibrinolysis in clinical practice.

INTRA-ARTERIAL FIBRINOLYSIS AND BRIDGING THERAPY

The PROACT II study provides the best evidence that intra-arterial fibrinolysis can improve patient outcomes (Furlan et al., 1999). This was a rigorously designed, multi-center (54 centers in USA and Canada), randomized, open-label study with blinded outcome assessment which enrolled 180 patients with angiographically proven middle cerebral artery occlusion and stroke symptoms for less than 6 h to receive intra-arterial pro-urokinase over 2 h plus intravenous heparin versus intravenous heparin alone (all patients received heparin for 4 h). Mechanical disruption of the clot was not allowed. Intra-arterial fibrinolysis resulted in recanalization in 66% of cases. Favorable functional outcome (defined as modified Rankin score of ≤ 2) at 90 days occurred in 40% of patients treated with intra-arterial fibrinolysis versus 25% of patients in the control group ($P = 0.04$; number needed to treat = 7). These results were quite remarkable considering that participating patients had severe deficits at presentation (median NIHSS = 17). The rate of symptomatic intracranial hemorrhage was 10% among patients treated with the fibrinolytic agent (versus 2% among controls), but there were no differences in mortality. Following the conclusion of the study, pro-urokinase was not approved for clinical use in stroke and its manufacturer stopped producing it. Over the subsequent years, clinical use of intra-arterial rt-PA has been found to be safe.

The Japanese MELT study had a similar design to PROACT II, albeit using urokinase as the fibrinolytic agent (Ogawa et al., 2007). It was prematurely aborted after enrollment of 114 patients because of the approval of intravenous rt-PA treatment in Japan. Clinical outcomes were more favorable with intra-arterial fibrinolysis, especially in terms of the number of patients achieving excellent function and minimal or no deficits at 90 days. Symptomatic intracranial hemorrhage occurred in 9% of fibrinolyzed patients (versus 2% of controls).

The combined results of PROACT II and MELT provide strong support for the clinical use of intra-arterial fibrinolysis. However, the advent of mechanical embolectomy afforded by the introduction of clot retrieving and suctioning catheters has changed the field. Today, endovascular reperfusion procedures start with attempts to remove the clot and fibrinolysis is usually only attempted as an adjuvant therapy when the clot cannot be mechanically retrieved or suctioned.

MECHANICAL THROMBECTOMY IN STROKE

After initial initiative by Zeumer's local thrombolysis in 1981 MT has been performed for many years with several devices without a widespread use of any of specific method. later, the MERCI device received FDA-approval in 2004 to "remove blood clots from the brain in patients experiencing an ischemic stroke" since then, more remarks was pooled from more and more data analysis; with conclusion that It is not simple as just "remove blood clots" but other factors should be considered; like possible target populations characteristics for mechanical recanalisation (Nogueira and Smith 2009), the impact of time for recanalisation (Fields, Lutsep et al. 2011) and the relation of recanalisation to the vessel occlusion site (Shi, Loh et al. 2010).

Mechanical recanalisation techniques can be divided by their working principle into three major approaches: proximal, distal thrombectomy and stent retrievers.

PROXIMAL THROMBECTOMY

The Penumbra System (Penumbra, Alameda, USA) is just modification of the manual proximal aspiration technique (Chapot, Houdart et al. 2002; Kang, Hwang et al. 2011) and consists of a dedicated reperfusion catheter connected to a pumping system applying continuous aspiration. The system was FDA approved for acute stroke treatment in 2007. The Penumbra System has been investigated in several trials. In the Penumbra Pivotal Stroke Trial (2009) recanalisation of the target vessel was successful in 81.6 % of patients with comparably high (32.8 %) mortality and good outcome in 29 % of patients with recanalisation of the target vessel. This poor clinical outcome despite the relatively high recanalisation rate in this trial prompted discussion of the impact of recanalisation using mechanical thrombectomy. Kulcsar et al. (Kulcsar, Bonvin et al. 2010) who reported successful recanalisation in 93 % of 27 patients with large vessel occlusion (mean NIHSS 14) and good clinical outcome in 48 % with a mortality rate of 11 %. Mean procedure time was 1.6 h. Consequently he focused more attention on the importance of "rapid recanalization" procedure is the key for better outcome.

DISTAL THROMBECTOMY

The distal approach has been shown to be more effective in in-vivo experimental studies compared to proximal manual aspiration (Brekenfeld, Schroth et al. 2008). However, Compared to proximal thrombectomy approaches, former is technically more challenging. Whereas a first step, the occlusion site has to be crossed with a microcatheter in order

to deliver the device distally to the thrombus. After Merci device (Concentric Medical, USA), the first FDA approved distal thrombectomy device, several distal thrombectomy devices have been introduced into clinical practice.

The MERCI trial (Smith, Sung et al. 2005) achieved a successful recanalisation in 46 % with good clinical outcome in 27.7 % of patients. Mean procedure time was 2.1 h and clinically significant procedural complications occurred in 7.1 %. The subsequent Multi-MERCI trial (Smith, Sung et al. 2008) in contrast to the MERCI trial, IV rtPA, IAT or other mechanical treatment approaches were allowed in addition to the Merci device, and new modified versions of the Merci device were included. Successful recanalisation was achieved in 57.3 % using the Merci retriever alone and in 69.5 % using additional recanalisation modalities. Overall, favorable clinical outcome was achieved in 36 %. Mean procedure time was 1.6 h, with clinically significant procedural complications in 5.5 % and sICH in 9.8 %.

ENDOVASCULAR TEMPORARY BYPASS

The most recently introduced mechanical treatment approaches are "Endovascular temporary bypass" or stent retriever. Stent retrievers are self-expandable, re-sheathable and re-constrainable stent-like thrombectomy devices. The concept of stent retriever combines the advantages of intracranial stent deployment with immediate flow restoration and a thrombectomy device with definitive clot removal from the occluded artery. Being retriever ; means complete removal of the device and avoiding the major disadvantages associated with permanent stent implantation, such as the need for double anti-platelet medication which potentially increases the risk of hemorrhagic complications (Zaidat, Wolfe et al. 2008) and the risk of in-stent thrombosis or stenosis .

Application is comparable to that of intracranial stents. The radial force of the stent retriever is able to immediately generate a channel by compressing the thrombus and to partially restore blood flow to the distal territory in most cases, creating a channel for a temporary bypass. However, the device is typically left in place for an embedding time up to 10 min allowing engagement of the thrombus within the stent struts (Brekenfeld, Schroth et al. 2011). In-vivo experimental studies have illustrated incorporation of the thrombus within the stent struts. During mobilization and retrieval of the device, the thrombus-device complex remains in a straight position without obvious compression or elongation of the clot material (Brekenfeld, Schroth et al.

2011). This might result in an increased retrieval force required to mobilize the thrombus and lower retrieval success rate (Brekenfeld, Schroth et al. 2008). Therefore, straight thrombus position during retrieval and firm clot engagement appear to be key features of stent retrievers compared to the mechanical principle of action of other thrombectomy devices and may explain their high success rates (Brekenfeld, Schroth et al. 2011).

Bridging therapy consists of administering intravenous fibrinolysis and then proceeding to endovascular treatment if the patient fails to improve and there is persistent major intracranial vessel occlusion. The IMS II trial tested this strategy on 81 stroke patients with severe deficits at presentation (median NIHSS of 19) (The IMS II Trial Investigators, 2007). Intravenous rt-PA (0.6 mg/kg) was started within 3 h and intra-arterial rt-PA (up to 22 mg) within 5 h of symptom onset. Patients treated in this multi-center, open-label, single arm pilot study had better outcomes than the rt-PA-treated patients in the NINDS study despite longer time to start of intravenous fibrinolysis and much worse initial stroke severity. The rate of symptomatic intracranial hemorrhage was nearly 10%, but 3 month mortality was actually lower than expected (16%).

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