12.1 Rationale

Stroke remains the third most common cause of death in the industrialized nations, after myocardial infarction and cancer, and the single most common reason for permanent disability [1]. In 1996, the Food and Drug Administration (FDA) approved intravenous (i.v.) thrombolysis with recombinant tissue plasminogen activator (rt-PA, alteplase) for the treatment of acute ischemic stroke after reviewing the results of the National Institute of Neurological Disorders and Stroke (NINDS) and rt-PA Stroke Study Group trial [2]. Intravenous rt-PA thrombolysis was the first approved treatment for acute stroke that effectively treats the causative vascular occlusion. This strategy has the advantage of being relatively easy and rapid to initiate, and does not require specialized equipment or highly technical expertise. Even though thrombolysis was initially a matter of relative controversy, its benefits are now unquestionable. A Cochrane Database Review included 18 trials (16 double-blind) with a total of 5727 patients who received thrombolytics [i.v. urokinase, streptokinase, rt-PA or recombinant intra-arterial (i.a.) pro-urokinase] up to 6 h after ischemic stroke. The review showed a significant reduction in the proportion of patients who were dead or dependent (modified Rankin 3–6) at the end of follow-up at 3–6 months [odds ratio (OR) 0.84, 95% confidence interval (CI) 0.75–0.95] despite a significant increase in the odds of death within the first 10 days (OR 1.81, 95% CI 1.46–2.24), most of which were related to symptomatic intracranial hemorrhage (OR 3.37, 95% CI 2.68–4.22) [3]. Moreover, a recent pooled analysis of
six major randomized placebo-controlled i.v. rt-PA stroke trials (ATLANTIS I and II, ECASS I and II, and NINDS I and II), including 2775 patients who were treated with i.v. rt-PA or placebo within 360 min of stroke onset, suggested a potential benefit beyond 3 h, even though the chances of a favorable 3-month outcome decreases as the interval from stroke onset to start of treatment increases.

However, i.v. rt-PA is not a panacea for acute stroke treatment. Indeed, the recanalization of proximal arterial occlusion by i.v. rt-PA ranges from 10% for internal carotid artery (ICA) occlusion to 30% for proximal middle cerebral artery (MCA) occlusion [4]. Analysis of the NINDS data shows only a 12% absolute increase in good outcomes between the placebo and rt-PA group at 3 months [5]. In other words, eight stroke patients must be treated with rt-PA to achieve one additional good patient outcome. However, this analysis understates the impact of rt-PA on stroke patients because it fails to include the patients who partially improved [6]. Even when considering this argument, rates of improvement are far from ideal and, given the prevalence and impact of acute ischemic stroke, it is imperative to devise strategies that can be more effective.

Local i.a. thrombolysis (IAT) has several theoretical advantages over i.v. thrombolysis. For instance, by using coaxial microcatheter techniques, the occluded intracranial vessel is directly accessible and the fibrinolytic agent can be infused into the thrombus. This allows a smaller dose of fibrinolytic agent to reach a higher local concentration than that reached by systemic infusion. With the smaller dose, complications from systemic fibrinolytic effects, including intracranial hemorrhage, can theoretically be reduced.

Moreover, thrombolytics need only be given for as long as the vascular occlusion persists, avoiding exposure to unnecessary higher doses. For these reasons, the treatment window for endovascular lysis can be extended over the typical i.v. window of 3 h. Another major advantage is the combination of thrombolytic treatment with mechanical manipulation of the clot, which may improve recanalization rates [7]. Indeed, mechanical lysis with little or no thrombolytic agent has emerged as a key option for patients who either have a contraindication to thrombolytics (e.g., recent surgery) or are late in their presentation [8, 9]. Furthermore, adjunctive endovascular treatment may be essential for the accomplishment of a successful thrombolysis; for example, through stenting of a dissected vessel, or through angioplasty with or without stenting of an occlusive lesion [10–12].

The major disadvantages to the endovascular strategy include the delay in initiating treatment because of the logistics of doing an angiogram, the additional risks and expense of an invasive procedure, and the fact that this therapy is not available in many communities.

12.2 Technical Aspects

The Massachusetts General Hospital (MGH) protocol for IAT in acute stroke, including inclusion and absolute exclusion criteria, relative contraindications, pre- and post-thrombolysis work-up and management, and management of symptomatic intracranial hemorrhage (ICH) after thrombolysis, is described in the Appendix at the end of this chapter.

Fig. 12.1 a–i

A 74-year-old female presenting with sudden onset of left hemiparesis, right gaze deviation and slurred speech. a Non-contrast head CT showed a “hyperdense MCA sign” on the right. b, c CTA demonstrated a proximal right MCA cut-off. d CT perfusion showed reduction in cerebral blood flow (CBF) with e prolongation of mean transit time (MTT) and f relative preservation of cerebral blood volume (CBV) in the right MCA territory consistent with a salvable ischemic penumbra (CBF/CBV “mismatch”). g Angiogram confirmed proximal MCA occlusion with good collateral flow. h Complete recanalization occurred post intra-arterial thrombolysis (IAT) with 2.6 mg of rt-PA and wire manipulation. i Follow-up MRI demonstrated a right MCA infarct involving the deep nuclei but sparing the cortex. This frequently happens with occlusions proximal to the lenticulostriate vessels, given the poor collateral flow to this territory.
12.2.1 Pre-procedure Evaluation and Patient Monitoring

After clinical and imaging evaluation suggests the need for IAT, the anesthesia team is contacted and informed of the patient’s estimated time of arrival at the interventional neuroradiology suite. Patients referred from other institutions who have had ICH and infarcts greater than one-third of the involved vascular territory excluded by outside CT may receive i.v. t-PA before transfer and while en route as part of a “bridging” approach [13]. When CT/CT angiography (CTA) confirms the presence of a large vessel occlusion, the patient is brought emergently to angiogra-
phy. Soft-copy review of noncontrast CT with variable window width and center level settings to accentuate the contrast between normal and edematous tissue (e.g., width 30, level 30) may optimize the recognition of early ischemic changes [14]. We consider the presence of hypodensity involving greater than one-third of the affected vascular territory a contraindication for thrombolysis [15]. Review of post-contrast CTA source images provides a good estimative of whole-brain perfusion without the delay required to process the conventional CT perfusion images [16]. However, if time allows, CT perfusion maps can more accurately characterize the ischemic penumbra (Figs. 12.1, 12.2) [17]. Careful but expedited pre-procedural analysis of the CTA may be extremely helpful in establishing the presence of anatomic variants (e.g., bovine aortic arch) or pathological states (e.g., vessel origin or bifurcation disease) prior to the catheterization procedure. Concurrently, the team Neurologist and/or interventional Neuroradiologist obtain consent while other team members prepare the patient for the procedure.

MRI with MRA, as well as diffusion- and perfusion-weighted imaging (DWI/PWI), has the advantage of providing more complete information on brain parenchymal injury and penumbra at risk. However, it is important that the MRI is performed in a manner that does not significantly delay the endovascular therapy. Nonetheless, MRI can be particularly helpful in selected difficult cases. Patients who present with seizures at stroke onset, a contraindication to i.v. t-PA in the NINDS trial, may need to undergo MRI to exclude the possibility of post-ictal Todd’s paralysis unless vascular occlusion is clearly seen on CTA [18]. Similarly, in other situations such as complex migraine, functional disorder, transient global amnesia, acute demyelination, amyloid angiopathy, and brain tumor, the diagnostic abilities of MR can be useful in distinguishing a stroke mimic from an acute ischemic stroke [19]. It should be noted, however, that prolonged seizures and acute demyelination can also cause restricted diffusion. We and others have found that DWI lesions can be partially reversed by IAT in as many as 19% of cases [20, 21]. The application of DWI and PWI in the extension of the therapeutic time window for acute stroke is currently under investigation [22, 23].

A sterile angiography equipment tray should always be prepared at the end of each workday for emergency use after hours to save time during set up. The patient is placed on a cooling blanket to induce moderate hypothermia for brain protection while on the angiography table. Stroke patients are often confused, uncooperative, and combative, which makes digital subtraction angiography and microcatheterization difficult. In addition, access to the patient is limited within the biplane angiographic unit making airway management problematic. The major disadvantage of general anesthesia is the inability to monitor neurological status during the procedure. In most cases the induction of general anesthesia requires only a few minutes and can be performed in tandem with other steps of patient preparation. In addition to giving general anesthesia, the Anesthesiologist also controls patient monitoring [blood pressure (BP) management, airway management, and anticoagulation], leaving the interventional Neuroradiologist free to concentrate on the technical aspects of the procedure.

A radial arterial line and Foley catheter are placed if time and manpower permit. Alternatively, blood pressure can be monitored via the femoral arterial sheath. Immediately prior to the induction of general anesthesia, the patient’s neurological status is reassessed. If deficits have resolved or are rapidly improving, the procedure should be aborted. Mild induced hypertension (systolic 140–160 mmHg) can maximize cerebral perfusion via leptomeningeal collaterals or through a partial occlusion. However, severe hypertension should be avoided and promptly treated. Sustained systolic BP over 180 mmHg and/or diastolic BP over 110 mmHg is considered a contraindication to thrombolysis. Large bore peripheral access is recommended over central venous catheterization. If central venous access is necessary, a femoral venous catheter can be inserted preferably under fluoroscopy. Both groins should be prepared in standard sterile fashion. The best pulse should be used for arterial access. A micropuncture kit should be used to obtain arterial and venous access in patients who are about to receive or have already received thrombolytics.
12.2.2 Procedural Technique

12.2.2.1 Chemical Thrombolysis

A long flexible sheath should be used to obviate difficult catheterizations in patients with tortuous iliac vessels. Typically, a 5 or 6 French guide catheter with a large inner diameter is used, but if angioplasty or stenting of the cervical vessels is anticipated, an 8 or 9 French catheter may be required. The guide catheter should be placed in the vessel of interest without delay (the Circle of Willis and pial collaterals have been previously evaluated by CTA). After a baseline angiogram confirms the presence and location of vascular occlusion, a wire-guided end hole microcatheter (e.g., Prowler microcatheter – Cordis Neurovascular, Miami Lakes, Fla., USA) is navigated into the face of the clot. The microwire is used to gently traverse the clot. Care must be taken in this essentially blind manipulation to avoid vascular perforation or dissection. Hand injection of a small amount of contrast can be performed to define the distal end of the clot. Once the microcatheter is advanced beyond the clot, thrombolytic infusion begins – the microcatheter is pulled back through the clot while drug is infused. Urokinase (UK) comes in powder form and the dosage is measured in units. It is best to reconstitute the powder (250,000 units per vial) in 5 ml of sterile water solution. This solution is then further diluted in 45 ml of normal saline to obtain a final concentration of 5,000 units/ml. The mixture should be slowly mixed to avoid foaming. UK is injected with 1-ml syringes as the microcatheter is pulled slowly back through the thrombus. This manipulation laces the clot with UK and is repeated several times, crossing the clot with the microcatheter and microwire. After the first pass, the arterial anatomy is better understood and more aggressive manipulations with the microwire can be made to mechanically disrupt the clot. We infuse UK at a rate of approximately 10,000 units/min (600,000 units/h). Rough adjustments are made depending on the clinical circumstances and imaging findings.

The interventional Neuroradiologist should limit the number of angiograms and microcatheter injections performed during the exam. Direct injection of contrast into stagnant vessels, which have injured glial cells, and breakdown of the blood–brain barrier may result in contrast extravasation. Contrast is readily visualized on immediate post-thrombolysis CT as an area of high attenuation in the parenchyma. In some instances, MRI with susceptibility sequence may be necessary to differentiate contrast extravasation from ICH [24]. This may be of particular importance in patients who need early anticoagulation or antiplatelet therapy. The area of contrast stain appears to correlate with the location of eventual infarct.

Despite the direct infusion of UK into the thrombus, clot disintegration requires an average of 90 min with traditional thrombolytic infusion and moderate microwire mechanical manipulation. Recanalization is frequently seen using UK at doses around 750,000 units but the amount of time and thrombolytic needed for recanalization varies according to the age and nature of the thrombus. Freshly formed thrombi usually dissolve easily, but thrombus that has embolized from the heart or from other sources may be older and more resistant to lysis.

Once bulk antegrade flow is restored, it may be necessary to lyse distal emboli in clinically significant territories, which requires repositioning of the microcatheter. Successful recanalization should be based on guide catheter injections rather than microcatheter injections since superselective injections may incorrectly demonstrate antegrade flow even though the vessel is still occluded on guide catheter angiograms. The infusion is terminated when adequate antegrade flow is restored, or the predetermined time limit or maximal dose limit is reached. Ominous signs such as contrast extravasation should prompt immediate termination of drug infusion, followed by the appropriate management steps. Treatment of anterior circulation ischemia should occur within 6 h of ictus or before using more than 1,250,000 units of UK in patients who have not received i.v. t-PA, or before using more than 500,000 units of UK in patients who have received i.v. t-PA. There is no specific time window for posterior circulation ischemia treatment, but dosages of UK are limited to 1,500,000 units.

Fibrinolytic agents have several disadvantages. First, although direct infusion maximizes the local drug concentration, dissolution of a clot takes an extended period of time, and time is critical in preserving the penumbra. Second, fibrinolytics increase
the risk of hemorrhage locally within the brain or systemically. Lastly, not all thromboembolic occlusions can be lysed with thrombolytic drugs. This resistance to enzymatic degradation may be related to excessive cross-linking in mature embolic clots, or to emboli composed of cholesterol, calcium, or other debris from atherosclerotic lesions. In others, the lack of flow may result in decreased delivery of circulating plasminogen, allowing the high concentration of fibrinolytic to quickly deplete the available plasminogen. This local plasminogen deficiency would result in impaired fibrinolytic activity [25].

12.2.2 Mechanical Thrombolysis

Mechanical thrombolysis has several advantages over chemical thrombolysis and may be used as a primary or adjunctive strategy. First, it lessens and may even preclude the use of thrombolytics, in this manner reducing the risk of ICH. Second, by avoiding the use of thrombolytics it may be possible to extend the treatment window beyond 6 h. Third, mechanically fragmenting a clot increases the surface area accessible to fibrinolytic agents and allows inflow of fresh plasminogen, which in turn increases the speed of lysis.
Finally, clot retrieval devices may provide faster re-
canalization and may be more efficient at coping with
material resistant to enzymatic degradation.

Currently, there are several techniques available
for mechanical thrombolysis. The most common is
the use of probing the thrombus with the microgu-
dewire. This technique useful in facilitating chemical
thrombolysis (Fig. 12.3) [7]. Alternatively, a snare
(e.g., Amplatz Goose-Neck Microsnare, Microvena,
White Bear Lake, Minn., USA) can be used for multi-
ple passes through the occlusion to disrupt the
thrombus [26]. A snare can also be used for clot re-
trieval, mostly in situations where the clot has a firm
consistency or contains solid material [27]. Inflation
of soft balloons in the proximal vessels may reduce or
reverse flow and facilitate the clot extraction [9]. Bal-
loon-assisted thrombolysis has gained wide accept-
ance with the advent of the newer and more compli-
ant balloons (Fig. 12.4). However, the risks of vascu-
lar rupture and distal emboli cannot be underesti-
mated and we reserve this technique for patients
whose flow cannot be restored by more conservative
means. Indeed, when underlying atherosclerotic
lesions are found after clot lysis, the need for angio-

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**Fig. 12.4 a–f**

An 88-year-old male presenting with sudden onset of right hemiparesis, left gaze deviation and aphasia. Angiography
demonstrated complete occlusion of the M1 segment of the left MCA (a, b). Recanalization of the left MCA (e, f) was
accomplished after i.a. infusion of 450,000 units of urokinase and angioplasty using a Hyperglide balloon (c, d). d Note
the circumferential “waisting” of the balloon, likely related to a previous existing stenosis. e Final angiogram showed mild
to moderate residual narrowing at that area.
plasty should be based upon the hemodynamic effects of the stenosis. If antegrade flow can be maintained with anticoagulation alone, angioplasty is not necessary in the acute phase. However, many stenoses reduce flow sufficiently and lead to re-thrombosis [12]. In these patients, angioplasty with or without stenting in concert with thrombolysis can be more effective in maintaining perfusion than thrombolysis alone [28–31]. The angioplasty balloon catheters we have used for mechanical thrombolysis include the Sentry (Boston Scientific, Fremont, Calif., USA) and Hyperglide (Micro Therapeutics, Irvine, Calif., USA). Antegrade flow is essential for the maintenance of vessel patency. This is particularly evident in patients...
with severe proximal (cervical) stenosis; it is common for these patients to develop re-thrombosis after vessel recanalization. These patients may also benefit from angioplasty and/or stenting of the proximal lesion in addition to thrombolysis of the distal vessels (Fig. 12.5) [10].

The disadvantages of clot removal include the technical difficulty of navigating mechanical devices into the intracranial circulation, excessive trauma to the vasculature, and fragmented thrombus causing distal emboli. Nonetheless, the advantages of mechanical thrombolysis appear to outweigh these disadvantages.

### 12.2.2.3 New Mechanical Devices

The **Concentric Retriever** (Concentric Medical, Mountain View, Calif., USA), a flexible, tapered Nitinol wire with a helical tip that is used in conjunction with a balloon guide catheter and a microcatheter, is the only device currently approved by the FDA for the endovascular treatment of stroke patients (Fig. 12.6). The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Trial involved the use of this device in 141 patients with occlusion involving the ICA, the M1 segment of the MCA, or the basilar or vertebral arteries, within 8 h of symptoms onset. None of the patients were eligible for i.v. thrombolysis. Interim data from this trial showed that 47% of patients treated only with the device were successfully recanalized. Of those patients, about half had good functional outcomes measured at 90 days post treatment [8].

The **EKOS MicroLys US infusion catheter** (EKOS, Bothell, Wash., USA) is a 2.5 F standard microinfusion catheter with a 2-mm, 2.1-MHz ring sonography transducer (average power, 0.21–0.45 W) at its distal tip that creates a microenvironment of ultrasonic vibration to facilitate thrombolysis. In a pilot study, where ten patients with anterior-circulation occlusions (mean NIHSS of 18.2) and four with posterior-circulation occlusions (mean NIHSS of 18.75) were treated with this device, TIMI 2–3 flow (for explanation of TIMI see Table 12.2) was achieved in 8 out of the 14 patients in the first hour. Average time to recanalization was 46 min. No catheter-related adverse events occurred [32].

The **EPAR** (Endovascular Photoacoustic Recanalization; Endovasix, Belmont, Calif., USA) is a mechanical clot fragmentation device based on laser technology. However, the emulsification of the thrombus is a mechanical thrombolysis and not a direct laser-induced ablation. The photonic energy is converted to acoustic energy at the fiberoptic tip through creation of microcavitation bubbles. In a recent study, where 34 patients (10 ICA, 12 MCA, 1 PCA, and 11 vertebrobasilar occlusions) with a median NIHSS of 19 were treated with EPAR, the overall recanalization rate was 41.1% (14/34). In 18 patients with vessel recanalization, complete EPAR treatment was possible in 11 patients (61.1%). The average lasing time was 9.65 min. Additional treatment with i.a. t-PA occurred in 13 patients. One patient had a vessel rupture resulting in fatal outcome. Symptomatic hemorrhages occurred in 2 patients (5.9%). The overall mortality rate was 38.2% [33].

The **Possis AngioJet system** (Possis Medical, Minneapolis, Minn., USA) is a rheolytic thrombectomy device that uses high-pressure saline jets to create a distal Venturi suction which gently agitates the clot face. The generated clot fragments are then sucked into the access catheter. A 5-French Possis AngioJet catheter has been used in our institution to successfully treat three patients who presented with acute stroke in the setting of ICA occlusion. Patency of the carotid artery was reestablished in two patients. In the third patient, the device was able to create a channel through the column of thrombus, allowing intracranial access [34].

### 12.2.2.4 Thrombolytic Agents

The thrombolytic drugs act by converting the inactive proenzyme plasminogen into the active enzyme plasmin. Plasmin can degrade fibrinogen, fibrin monomers, and cross-linked fibrin (as is found in thrombus) into fibrin(ogen) degradation products. These agents vary in stability, half-life, and fibrin selectivity. The thrombolytics that have been used for stroke IAT include urokinase (UK), alteplase,
reteplase, prourokinase (pro-UK), and streptokinase (SK) [26, 35]. In general, the nonfibrin-selective drugs (e.g., UK and SK) can result in systemic hypofibrinogenemia, whereas the fibrin-selective agents (e.g., rt-PA and rpro-UK) are only active at the site of thrombosis.

First-Generation Agents. Streptokinase, a protein derived from group C β-hemolytic streptococci, has a half-life of 16–90 min and low fibrin specificity. This drug is no longer used for stroke IAT. Urokinase is a serine protease with a plasma half-life of 14 min and low fibrin specificity. The UK dose used in cerebral IAT has ranged between $0.02 \times 10^6$ and $2 \times 10^6$ units [35]. UK was withdrawn from the market in 1999 but was approved for lysis of pulmonary embolism in 2003, and has again become the thrombolytic agent of choice for stroke IAT at our institution.

Second-Generation Agents. Alteplase (rt-PA) is a serine protease with a plasma half-life of 3.5 min and a high degree of fibrin affinity and specificity. The rt-PA dose used in cerebral IAT has ranged between 20 and $60 \text{ mg}$ [35]. The theoretical disadvantages of alteplase include its relatively short half-life and limited penetration in the clot matrix because of strong binding with surface fibrin, which could delay recanalization and increase the risk of recurrent occlusion. Pro-urokinase (rpro-UK) is the proenzyme precursor of UK. It has a plasma half-life of 7 min and high fibrin specificity. Despite the favorable results of the PROACT I and II trials, the FDA has not yet approved the use of rpro-UK.

Third-Generation Agents. Reteplase is a structurally modified form of alteplase, with a longer half-life (15–18 min). In addition, it does not bind as highly to fibrin; unbound reteplase can then penetrate the clot and potentially improve in vivo fibrinolytic activity. Qureshi et al. [26] have reported the use of low-dose i.a. reteplase (up to 4 units) in conjunction with mechanical thrombolysis [26]. TIMI 2 and 3 recanalization was achieved in 16 out of 19 patients, with no symptomatic ICH. Tenecteplase is another modified
form of rt-PA with a longer half-life (17 min), greater fibrin specificity, and greater resistance to plasminogen activator inhibitor-1 (PAI-1).

Desmoteplase is a genetically engineered version of the clot-dissolving factor found in the saliva of the vampire bat Desmodus rotundus. This drug is more potent and more selective for fibrin-bound plasminogen than any other known plasminogen activator. The i.v. administration of desmoteplase 3–9 h after symptoms onset in stroke patients who demonstrate a PWI–DWI mismatch on MRI is currently being investigated.

No direct comparison between the different thrombolytic agents has been made so far. In a retrospective review of the results for acute stroke IAT performed at our center, we found significantly higher rates of recanalization and good clinical outcome in the era in which i.a. UK was used versus the era in which UK was not available and IAT with rt-PA was the primary treatment [36]. Conversely, in another retrospective study, Eckert et al. [37] found no major difference between the recanalization rates of UK and rt-PA.

12.2.2.5 Adjunctive Therapy

Systemic anticoagulation with i.v. heparin during the peri-procedural phase of IAT has several potential advantages, including augmentation of the thrombolytic effect of some agents such as rpro-UK, prevention of acute re-occlusion, and a reduction of the risk of catheter-related embolism. However, these indications are counterbalanced by the potentially increased risk of brain hemorrhage when heparin is combined with a thrombolytic agent. We tend to utilize a regimen similar to the low-dose heparin regimen used in PROACT II (2000 units bolus and 500 units/h for 4 h), aiming for an activated clotting time (ACT) between 200 and 250 s. We avoid using heparin in cases of “bridging” therapy with i.v. rt-PA.

Argatroban and lepirudin are direct thrombin inhibitors. These agents should replace heparin in cases where the diagnosis of heparin-induced thrombocytopenia (HIT) type-II is confirmed or even suspected. HIT type II is an immune-mediated disorder characterized by the formation of antibodies against the heparin-platelet factor 4 complex, which results in thrombocytopenia, platelet aggregation, and the potential for arterial and venous thrombosis. The possibility of HIT type II should be raised in patients who demonstrate a platelet count drop to less than 100,000 per milliliter or by more than 50% from baseline, in the setting of heparin therapy (usually 5–12 days after initial exposure).

The use of glycoprotein (GP) IIb/IIIa antagonists, such as abciximab (ReoPro®) or eptifibatide (Integrilin®), in ischemic stroke is still investigational. No cases of major ICH were seen in a pilot, randomized, double-blind, placebo-controlled study where 54 patients presenting within 24 h after ischemic stroke onset were randomly allocated to receive escalating doses of abciximab [38]. Similarly, the Abciximab in Emergent Stroke Treatment Trial (AbESTT) demonstrated that intravenous abciximab can be administered with a reasonable degree of safety to patients with acute ischemic stroke within 6 h of symptoms onset. This trial also provided evidence that abciximab may increase the likelihood of a favorable outcome at 3 months. A phase III, multicenter, randomized, double-blind, placebo-controlled trial is currently being performed [39]. In addition, The NIH is currently sponsoring a phase II trial looking at intravenous reteplase in combination with abciximab for the treatment of ischemic stroke 3–24 h from onset. Preliminary analysis of the first 21 patients enrolled has revealed no symptomatic ICH or major hemorrhage [40]. The data for the use of GP IIb/IIIa inhibitors in conjunction with i.a. thrombolysis are even more scant and limited to case reports. Intravenous abciximab has been successfully used as adjunctive therapy to i.a. t-PA or UK in cases of acute stroke [41, 42]. In our institution, we have treated 24 acute stroke patients with i.a. t-PA (mean dosage: 12 mg) in combination with i.v. eptifibatide and found only one case of symptomatic hemorrhage (4.2%), which was related to a rupture during balloon angioplasty. Intra-arterial abciximab has been successfully employed to treated thromboembolic complications encountered during endovascular therapeutic procedures [43, 44]. At MGH, we have used i.a. infusion of eptifibatide at a concentration of 0.75 mg/ml in doses up to 6 mg to treat endovascular
complications with good results and no hemorrhagic complications, including a patient who also received 250,000 units of i.a. UK (Fig. 12.7). Depending on the nature of the thrombotic event we may maintain the patient on continuous i.v. infusion of eptifibatide for 24 h. Despite, the promising initial experience with Gp IIb/ IIIa antagonist, we recommend that these drugs should be used judiciously and under close monitoring.

12.3 Intra-arterial Thrombolysis Trials

12.3.1 Background

Similar to the experience with i.v. thrombolysis, the majority of early work on IAT has been reported in nonrandomized case series. Reports of successful IAT go back to the late 1950s, when Sussmann and Fitch [45] described the recanalization of an acutely occluded internal carotid artery with i.a. injection of plasmin. Nonetheless, it was not until the early 1990s that this approach was studied in a more systematic manner.

Lisboa et al. [35] analyzed the safety and efficacy of IAT on the basis of current published data. They found a total of 27 studies (including at least 10 patients in each) with a total of 852 patients who received IAT and 100 control subjects. There were more favorable outcomes in the IAT than in the control group (41.5% versus 23%), with a lower mortality rate for IAT (27.2% versus 40%). The IAT group had an odds ratio of 2.4 for a favorable outcome despite a higher frequency of symptomatic ICH (9.5% versus 3%). In addition, they found a trend towards better outcomes with combined i.v. t-PA and IAT than with IAT alone. They also remarked that IAT-treated supratentorial strokes are more likely to have favorable outcomes than the infratentorial ones (42.2% versus 25.6%).

12.3.2 Anterior Circulation Thrombolysis

The safety and efficacy of IAT in the anterior circulation has been evaluated in two randomized, multicenter, placebo-controlled trials. In the Prolyse in Acute Cerebral Thromboembolism (PROACT) I and II trials, patients with proximal MCA (M1 or M2 segment) occlusions within 6 h of symptom onset were treated with recombinant pro-urokinase (rpro-UK) or placebo [46, 47].

In the PROACT I trial, 26 patients with a median NIHSS of 17 were treated with rpro-UK and 14 patients with a median NIHSS of 19 with placebo, at a median of 5.5 h from symptom onset [46]. Patients in
the treatment group received 6 mg of i.a. rpro-UK over 2 h, and all patients received high- or low-dose i.v. heparin given as a bolus followed by a 4-h infusion at the time of the angiogram. Mechanical disruption of the clot was not allowed. Both the recanalization rates (TIMI 2 or 3 flow: 57.7% versus 14.3%) and the incidence of symptomatic ICH (15.4% versus 7.1%) were higher in the rpro-UK than in the placebo group. Of note, all patients in the rpro-UK group with early CT changes involving >33% of the MCA territory suffered ICH. In the rpro-UK group, the rates of recanalization were dependent upon the administered dose of heparin. At the end of the 2-h rpro-UK infusion, 81.8% of the patients treated with high-dose heparin (100 IU/kg bolus followed by 1000 IU/h infusion for 4 h) demonstrated recanalization whereas only 40% were recanalized in the low-dose heparin subgroup (2000 IU bolus, followed by a 500 IU/h infusion for 4 h). However, the rate of symptomatic ICH at 24 h was also higher in the high-dose heparin group (27.3% versus 6.7%). The overall 90-day cumulative mortality was 26.9% in the rpro-UK group and 42.9% in the placebo group. While the number of patients in this study was too low to allow any definite conclusions regarding efficacy, its results led to the PROACT II trial.

The PROACT II trial was designed to assess the clinical efficacy and safety of i.a. r-proUK. In this study, 180 patients were enrolled in a 2:1 randomization scheme to receive either 9 mg i.a. r-proUK plus 4 h of low-dose i.v. heparin or low-dose i.v. heparin alone [47]. The primary clinical outcome, the proportion of patients with slight or no disability at 90 days (modified Rankin Score of ≤2), was achieved in 40% of the 121 patients in the rpro-UK treatment group as compared to 25% of the 59 patients in the control group (absolute benefit 15%, relative benefit 58%, number need = 7; *P*=0.04). The recanalization rate (TIMI 2 and 3) was 66% for the r-proUK group and 18% for the control group (*P*<0.001). Symptomatic ICH within 24 h occurred in 10% of r-proUK patients and 2% of control patients (*P*=0.06). All symptomatic ICH occurred in patients with a baseline NIHSS score of 11 or higher (NIHSS 11–20, 11%; NIHSS >20, 13%). Mortality after symptomatic ICH was 83% (10/12 patients). Blood glucose was significantly associated with symptomatic ICH in rpro-UK-treated patients (patients with baseline glucose >200 mg/dl experienced a 36% risk of symptomatic ICH compared with 9% for those with ≤200 mg/dl) [48].

Mortality was 25% for the rpro-UK group and 27% for the control group despite the higher incidence of ICH in the rpro-UK patients. Secondary clinical outcomes included the percentage of patients reaching an NIHSS score of <1, the percentage of patients achieving a 50% or greater reduction from baseline NIHSS, and the percentage of patients achieving a Barthel index score of 60 or greater and a Barthel index score of 90 or greater, all measured at 90 days. Despite a trend in favor of the rpro-UK group, none of these secondary functional or neurological outcome measures achieved statistical significance. Although encouraging, the results of PROACT II were not enough to grant the FDA approval of rpro-UK and another larger trial was requested.

Acute strokes due to carotid T occlusion carry a much worse prognosis than MCA occlusions. In a recent analysis of 24 consecutive patients (median NIHSS 19) presenting with T occlusions of the ICA, which was treated by IAT using urokinase at an average of 237 min from symptom onset, only 4 patients (16.6%) had a favorable outcome after 3 months. Partial recanalization of the intracranial ICA was achieved in 15 (63%), of the MCA in 4 (17%), and of the ACA in 8 patients (33%). Complete recanalization did not occur. The presence of good leptomeningeal collaterals and being younger than 60 years were the only predictors of a favorable clinical outcome [49]. New treatment strategies such as the combination of i.v. t-PA and IAT [50] or the use of new mechanical devices [34] may further improve the outcome in these patients.

### 12.3.3 Posterior Circulation Thrombolysis

No randomized, placebo-controlled studies of IAT for vertebrobasilar occlusion have yet been done and most of the rationale for its use is based on the favorable reports of uncontrolled case series (Table 12.1). Since the first series of IAT for basilar artery occlusion by Zeumer et al. in 1983 [51] approximately 278 cases have been reported, with an overall recanalization-
tion rate of 60%, and a mortality rate of 90% in non-recanalized patients and 31% in at least partially recanalized patients [52]. In general, distal occlusions, which are usually embolic, have higher recanalization rates than proximal occlusions, which are more commonly atherothrombotic. Most stroke experts agree that the time window for IAT in the posterior circulation should be longer than the one for strokes in the carotid circulation. The underlying principles for such an approach include not only the extremely poor prognosis of untreated lesions, with a mortality rate as high as 90%, but also a lower rate of hemorrhagic transformation in this vascular territory. In our institution, we typically treat basilar occlusion up to 12 h after symptoms onset. We consider an extension of this window to up to 24 or 48 h for patients with fluctuating symptoms or small infarcts on diffusion MRI.

### 12.3.4 Combined Intravenous and Intra-arterial Thrombolysis

Four studies have evaluated the feasibility, safety, and efficacy of combined i.v. rt-PA at a dose of 0.6 mg/kg and IAT in patients presenting with acute strokes within 3 h of symptom onset [13, 53–55]. This approach has the potential of combining the advantages of i.v. rt-PA (fast and easy to use) with the advantages of IAT (titrated dosing, mechanical aids to recanalization, and higher rates of recanalization), thus improving the speed and frequency of recanalization.

The Emergency Management of Stroke (EMS) Bridging Trial was a double-blind, randomized, placebo-controlled multicenter Phase I study of i.v. rt-PA or i.v. placebo followed by immediate IAT of rt-PA [53]. Seventeen patients were randomly assigned into the i.v./i.a. group and 18 into the placebo/i.a. group. Clot was found in 22 of 34 patients. TIMI 3 flow recanalization occurred in 6 of 11 i.v./i.a. patients versus 1 of 10 placebo/i.a. patients (P=0.03) and correlated to the total dose of rt-PA (P=0.05). However, no difference in the 7- to 10-day or the 3-month outcomes was found, and there were more deaths in the i.v./i.a. group. Eight ICHs occurred: all hemorrhagic infarctions. Symptomatic ICH occurred in one placebo/i.a. patient and two i.v./i.a. patients. Life-threatening bleeding complications occurred in two patients, both in the i.v./i.a. group.

The Interventional Management of Stroke (IMS) Study was a multicenter, open-labeled, single-arm pi-
lot study where 80 patients (median NIHSS 18) were enrolled to receive i.v. rt-PA (0.6 mg/kg, 60 mg maximum, 15% of the dose as a bolus with the remainder administered over 30 min) within 3 h of stroke onset (median time to initiation: 140 min) [13]. Additional rt-PA was subsequently administered via a microcatheter at the site of the thrombus up to a total dose of 22 mg over 2 h of infusion or until thrombolysis in 62 of the 80 patients. Primary comparisons were with similar subsets of placebo- and rt-PA-treated subjects from the NINDS rt-PA Stroke Trial. The 3-month mortality in Interventional Management Study (IMS) subjects (16%) was numerically lower but not statistically different than the mortality of placebo (24%) and rt-PA-treated subjects (21%) in the NINDS rt-PA Stroke Trial. The rate of symptomatic ICH (6.3%) in IMS subjects was similar to that of rt-PA-treated subjects (6.6%) but higher than the rate in placebo-treated subjects (1.0%, \( P=0.018 \)) in the NINDS rt-PA Stroke Trial. IMS subjects had a significantly better outcome at 3 months than NINDS placebo-treated subjects for all outcome measures (odds ratios ≥2). For the 62 subjects who received i.a. rt-PA in addition to i.v. t-PA, the rate of complete recanalization (TIMI 3 flow) was 11% (7/62) and the rate of partial or complete recanalization (TIMI 2 or 3 flow) was 56% (35/62).

Ernst et al. [54] performed a retrospective analysis of 20 consecutive patients (median NIHSS 21) who presented within 3 h of stroke symptoms and were treated using i.v. rt-PA (0.6 mg/kg) followed by i.a. rt-PA (up to 0.3 mg/kg or 24 mg whichever is less, over a maximum of 2 h) in 16 of the 20 patients. Despite a high number of ICA occlusions (8/16), TIMI 2 and 3 recanalization rates were obtained in 50% (8/16) and 19% (3/16) of the patients, respectively. One patient (5%) developed a fatal ICH. Ten patients (50%) recovered to a modified Rankin Scale (mRS) of 0 or 1; three patients (15%), to an mRS of 2; and five patients (25%), to an mRS of 4 or 5.

Suarez et al. [55] studied “bridging” therapy in 45 patients using i.v. t-PA at 0.6 mg/kg within 3 h of stroke onset. Patients exhibiting evidence of PWI–DWI mismatches on MRI underwent subsequent IAT. Eleven patients received IAT with rt-PA (maximal dose 0.3 mg/kg) and 13 patients received IAT with UK (maximal dose 750,000 units). Symptomatic ICH occurred in 2 of the 21 patients in the i.v. rt-PA-only group, but in none of the patients in the i.v. rt-PA/IAT group. Out of the 24 patients in the i.v. rt-PA/IAT group, 21 had MCA occlusions, 2 had ACA occlusions and 1 had PCA occlusion. Complete recanalization occurred in 5 of the 13 patients treated with i.v. rt-PA/i.a. UK and 4 of the 11 treated with i.v. rt-PA/i.a. rt-PA. Favorable outcomes (Barthel index 95) were seen in 92%, 64%, and 66% of the i.v. rt-PA/i.a. UK, i.v. rt-PA/i.a. rt-PA, and i.v. rt-PA-only groups, respectively.

A “reversed bridging” approach has been proposed by Keris et al. [56]. In this study, 12 patients (3 ICA occlusions and 9 MCA occlusions) out of the 45 enrolled patients (all with NIHSS >20) were randomized to receive an initial i.a. infusion of 25 mg rt-PA over 5–10 min followed by i.v. infusion of another 25 mg over 60 min, within 6 h of stroke onset (total combined dose 50 mg with a maximal dose of 0.7 mg/kg). The remaining 33 patients were assigned to a control group and did not undergo any thrombolysis. TIMI 2 and 3 recanalization occurred in 1/12 and 5/12 of the patients, respectively. None had symptomatic ICH. At 12 months, 83% of the patients in the thrombolysis group were functionally independent whereas only 33% of the control subjects had a good outcome.

In a prospective, open-label study, Hill et al. [57] assessed the feasibility of a “bridging” approach using full-dose i.v. rt-PA [57]. Following i.v. infusion of 0.9 mg/kg rt-PA, six patients underwent IAT with rt-PA (maximum 20 mg) and one underwent intracranial angioplasty. TIMI 2 or 3 recanalization was achieved in three of these patients. None had symptomatic ICH.

At our institution, we have treated 18 patients (mean NIHSS 17.4) with a full (0.9 mg/kg) i.v. rt-PA dose followed by IAT with rt-PA (mean dose 6 mg) [58]. We have achieved TIMI 2 or 3 recanalization in 72% of these patients with a symptomatic ICH rate of 16.7%. In our current “bridging” protocol, i.a. rt-PA has been replaced by i.a. UK.
Several grading systems have been developed as an attempt to quantify recanalization rates. The Thrombolysis in Myocardial Infarction (TIMI) grading system, either in its original or modified form (Table 12.2) [60], has been widely used. Another modification of the TIMI grading scheme was recently proposed by an Assessment Committee of the American Society of Interventional and Therapeutic Neuroradiology (Table 12.3) [61]. However, the aforementioned, classification systems are limited because they do not account for occlusion location or collateral circulation. Qureshi [62] has proposed a scheme based primarily on the occlusion site and degree of collateralization (Table 12.4). This scheme appears to have a strong correlation with the initial severity and in-hospital outcome of acute ischemic stroke [63].

The efficacy of i.v. thrombolysis is restricted by several factors including the relatively short therapeutic window, increased hemorrhagic rate, and poor recanalization rates as the clot burden is increased. IAT improves the rates of recanalization and good functional outcome in patients presenting with proximal occlusion of the intracranial arteries. Intravenous thrombolysis with rt-PA should be considered in patients presenting within 3 h of stroke onset as a “bridging” therapy to IAT. Mechanical thrombolysis has become a powerful adjunct to i.a. infusion of thrombolytics and should be considered as primary therapy in patients who have contraindications to thrombolytics or have late presentation (up to 8 h in the anterior circulation). The time window for IAT in the posterior circulation has not been well estab-
lished and, at this point, a judicious decision should be made on a case-by-case basis. The new neuroimaging techniques, including CT perfusion and MRI with DWI/PWI, have become essential in the decision-making process of thrombolysis. These methods may eventually define a subgroup of patients who will benefit from late thrombolysis.

Appendix: MGH Protocols for Intra-arterial Thrombolytics (Chemical and/or Mechanical) for Acute Stroke

Intra-arterial Inclusion Criteria

- A significant neurologic deficit expected to result in long-term disability, and attributable to large vessel occlusion (basilar, vertebral, internal carotid or middle cerebral artery M1 or M2 branches).
- Noncontrast CT scan without hemorrhage or well-established infarct. If MRI obtained, DWI–PWI mismatch with relatively small DWI abnormality (for example, less than one-third MCA territory).
- Acute ischemic stroke symptoms with onset or last known well clearly defined. Treatment within 6 h of established, nonfluctuating deficits due to anterior circulation (carotid/MCA) stroke. Treatment with mechanical thrombolysis using the Concentric Retriever device is a consideration in patients between 6 and 8 h of stroke symptom onset. The window of opportunity for treatment is less well defined in posterior circulation (vertebral/basilar) ischemia, and patients may have fluctuating, reversible ischemic symptoms over many hours or even days and still be appropriate candidates for therapy.

Absolute Exclusion Criteria

- Hemorrhage or well-established acute infarct on CT involving greater than one-third of the affected vascular territory.

### Table 12.4. Grades of increasing severity of arterial occlusion according to a new classification scheme. (ACA Anterior cerebral artery, BA basilar artery, ICA internal carotid artery, MCA middle cerebral artery, VA vertebral artery)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type of occlusion</th>
<th>BA and/or VA branch occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No occlusion</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>MCA occlusion (M3 segment)</td>
<td>ACA occlusion (A2 or distal segments)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥2</td>
</tr>
<tr>
<td>2</td>
<td>MCA occlusion (M2 segment)</td>
<td>ACA occlusion (A1 and A2 segments)</td>
</tr>
<tr>
<td>3</td>
<td>MCA occlusion (M1 segment)</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>Lenticulostriate arteries spared and/or leptomeningeal collaterals visualized</td>
<td></td>
</tr>
<tr>
<td>3B</td>
<td>No sparing of lenticulostriate arteries, and no leptomeningeal collaterals visualized</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>ICA occlusion (collaterals present)</td>
<td>BA occlusion (partial filling direct or via collaterals)</td>
</tr>
<tr>
<td>4A</td>
<td>Collaterals fill MCA</td>
<td>Anterograde filling$^a$</td>
</tr>
<tr>
<td>4B</td>
<td>Collaterals fill ACA</td>
<td>Retrograde filling$^a$</td>
</tr>
<tr>
<td>5</td>
<td>ICA occlusion (no collaterals)</td>
<td>BA occlusion (complete)</td>
</tr>
</tbody>
</table>

$^a$ Predominant pattern of filling
From Qureshi [62]
CNS lesion with high likelihood of hemorrhage status post chemical thrombolytic agents (e.g., brain tumors, abscess, vascular malformation, aneurysm, contusion).

Established bacterial endocarditis.

Relative Contraindications

- Mild or rapidly improving deficits.
- Significant trauma within 3 months.*
- CPR with chest compressions within past 10 days.*
- Stroke within 3 months.
- History of intracranial hemorrhage; or symptoms suspicious for subarachnoid hemorrhage.
- Major surgery within past 14 days.*
- Minor surgery within the past 10 days, including liver and kidney biopsy, thoracocentesis, lumbar puncture.*
- Arterial puncture at a noncompressible site within past 14 days (see below for femoral artery puncture).*
- Pregnant (up to 10 days postpartum) or nursing woman.*
- Suspected bacterial endocarditis.
- Gastrointestinal, urologic, or respiratory hemorrhage within past 21 days.*
- Known bleeding diathesis (includes renal and hepatic insufficiency).*
- Life expectancy <1 year from other causes.
- Peritoneal dialysis or hemodialysis.*
- PTT >40 s; platelet count <100,000/ml.*
- INR >1.7 (PT>15 if no INR available) with or without chronic oral anticoagulant use.*
- Seizure at onset of stroke. (This relative contraindication is intended to prevent treatment of patients with a deficit due to postictal Todd’s paralysis or with seizure due to some other CNS lesion that precludes thrombolytic therapy. If rapid diagnosis of vascular occlusion can be made, treatment may be given.)
- Glucose <50 or >400 mg/dl. (This relative contraindication is intended to prevent treatment of patients with focal deficits due to hypo- or hyperglycemia. If the deficit persists after correction of the serum glucose, or if rapid diagnosis of vascular occlusion can be made, treatment may be given.)

Pre-Thrombolysis Work-up

- Temperature, pulse, BP, respiratory rate.
- Physical exam/neurologic exam including NIHSS.
- 12-lead EKG.
- Complete blood count (CBC) with platelets, basic metabolic [electrolytes, blood urea nitrogen (BUN)/creatinine, glucose] and hepatic function panel, prothrombin time (PT, INR), partial thromboplastin time (PTT), erythrocyte sedimentation rate (ESR), fibrinogen. Blood for type and screen.
- Urine or blood pregnancy test in women of childbearing potential.
- Consider hypercoagulable panel in young patients without apparent stroke risk factors.

Pre-Thrombolysis Management

- Start supplementary oxygen. Treat any fever with acetaminophen. Nil by mouth (NPO) except medications.
- Do not place Foley, nasogastric tube, arterial line or central venous line unless it is absolutely necessary for patient safety.
- Do not lower blood pressure unless it is causing myocardial ischemia or exceeds 220/120 mmHg. Use labetolol i.v. (5–20 mg i.v. q 10–20 min) or, if necessary, sodium nitroprusside i.v. (0.5–10 µg/kg per min). Monitor with noninvasive cuff pressures q 15 min or continuous arterial pressure monitoring.
- Do not administer heparin unless recommended by the Acute Stroke Team.
- STAT head CT/CTA/CTP and possible MRI with DWI/PWI.
- Consider bypassing CTA if renal failure, diabetes, congestive heart failure. Hold metformin 48 h after iodinated contrast.

*Items marked with an asterisk may not be exclusions for mechanical thrombolysis with or without limited dose chemical agents.
Check patency of 16–18 gauge forearm i.v.
- Consider chest radiograph to exclude acute congestive heart failure or aortic dissection if clinical suspicion.
- Check MRI exclusions (e.g., severe claustrophobia, implanted pacemaker, metal fragments, shrapnel).
- Review CT/CTA with Interventionalist and Stroke Team.
- Obtain consent for procedure and general anesthesia in writing from patient or family.
- If time permits, obtain STAT DWI MR imaging but do not delay time to treatment.

Peri-Thrombolysis Management
- Confirm case with Anesthesia and consider starting heparin 3000-unit bolus and 800 units/h.
- Request orogastric or nasogastric tube placement prior to thrombolytic drug infusion.
- Induce moderate hypothermia (33–34 °C) during the case with cooling blanket.
- Consider induced hypertension until patency restored in patients with poor collateral flow.
- Consider terminating infusion of thrombolytic by 6 h in anterior circulation stroke. Consider early angioplasty at common carotid bifurcation or distal internal carotid bifurcation in selected cases.
- To prevent or treat acute re-occlusion or after angioplasty or stenting, consider i.v. eptifibatide.
- Call for CT scan to be done post thrombolysis en route to Neuro ICU. Repeat CT 6 h later, consider CTA if renal and cardiovascular function permits.
- Begin passive rewarming in Neuro ICU. Do not apply extra blankets or heating devices.
- If considering antiplatelet or anticoagulant agents, check fibrinogen >100 mg/dl and PTT <80 s.

Pre- and Post-Treatment Management
ICU admission for monitoring during first 24 h:
- Vital signs q 15 min for 2 h, then q 30 min for 6 h, then q 1 h for 16 h.
- Strict control of BP for 24 h per protocol.
- Neuro checks q 1 h for 24 h.
- Pulse oximeter; oxygen cannula or mask to maintain O₂ saturation >95%.
- Acetaminophen 650 mg p.o./p.r. q 4 h p.r.n. T >37 °C (99.4 °F); cooling blanket p.r.n. T >39 °C (102 °F), set to avoid shivering.
- No antiplatelet agents or anticoagulants in first 24 h.
- No Foley catheter, nasogastric tube, arterial catheter or central venous catheter for 24 h, unless absolutely necessary.
- STAT head CT for any worsening of neurologic condition.

Protocol for Blood Pressure Control After Thrombolysis
Patients will be admitted to the ICU for hemodynamic monitoring for a minimum of 24 h. A noninvasive blood pressure (BP) cuff is recommended unless sodium nitroprusside is required. BP will be strictly controlled according to the guidelines used in the NINDS trial as listed below. Clinical deterioration associated with acute reduction in BP should be evaluated immediately.

Monitor arterial BP during the first 24 h after starting treatment:
- Every 15 min for 2 h after starting the infusion, then
- Every 30 min for 6 h, then
- Every 60 min for 24 h after starting treatment.

If systolic BP is 180–230 mmHg or if diastolic BP is 105–120 mmHg for two or more readings 5–10 min apart:
- Give intravenous labetolol 10 mg over 1–2 min. The dose may be repeated or doubled every 10–20 min up to a total dose of 150 mg.
- Monitor BP every 15 min during labetolol treatment and observe for development of hypotension.

If systolic BP is >230 mmHg or if diastolic BP is in the range of 121–140 mmHg for two or more readings 5–10 min apart:
- Give i.v. labetolol 10 mg over 1–2 min. The dose may be repeated or doubled every 10 min up to a total dose of 150 mg.
Monitor BP every 15 min during the labetolol treatment and observe for development of hypotension.

If no satisfactory response, infuse sodium nitroprusside (0.5–10 μg/kg per min).

If diastolic BP is >140 mmHg for two or more readings 5–10 min apart:

- Infuse sodium nitroprusside (0.5–10 μg/kg per minute).
- Monitor BP every 15 min during infusion of sodium nitroprusside and observe for development of hypotension.
- Continuous arterial monitoring is advised if sodium nitroprusside is used. The risk of bleeding secondary to an arterial puncture should be weighed against the possibility of missing dramatic changes in pressure during infusion.

Management of Symptomatic Hemorrhage After Thrombolysis

- STAT head CT, if ICH suspected.
- Consult Neurosurgery for ICH.
- Check CBC, PT, PTT, platelets, fibrinogen and D-dimer. Repeat q 2 h until bleeding is controlled.
- Give fresh frozen plasma 2 units every 6 h for 24 h after dose.
- Give cryoprecipitate 20 units. If fibrinogen level <200 mg/dl at 1 h, repeat cryoprecipitate dose.
- Give platelets 4 units.
- Give protamine sulfate 1 mg/100 units heparin received in last 3 h (give initial 10 mg test dose i.v. slowly over 10 min and observe for anaphylaxis; if stable give entire calculated dose slow i.v.; maximum dose 100 mg).
- Institute frequent neurochecks and therapy of acutely elevated intracranial pressure (ICP), as needed.
- May give aminocaproic acid (Amicar®) 5 g in 250 ml normal saline i.v. over 1 h as a last resort.

References


58. Nogueira RG, Hoh BL, O’Donnell J, Pryor JC, Rabinov JD, Hirsch JA, Rordorf GA, Buonanno FS, Koroshetz WJ, Schwamm LH (2004) Safety of combined standard dose i.v. tPA (0.9 mg/Kg) followed by i.a. tPA vs. i.a. tPA alone in acute ischemic stroke: is dose reduction in bridging therapy necessary? Seventh Joint Meeting of the AANS/CNS Section on Cerebrovascular Surgery and the American Society of Interventional and Therapeutic Neuroradiology, February 2004, San Diego, Calif., USA


