

# Ischemic Stroke: Emergencies and Management

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## KEYWORDS

- Acute ischemic stroke • Thrombolytic therapy
- Cerebral angioplasty • Cerebral edema • Vascular dissection

It is now increasingly recognized that acute ischemic stroke is an emergent issue that is potentially amenable to interventions that may have a significant effect on outcome. Naturally, when one is talking about interventional therapy for acute ischemic stroke, outside of aspirin, there is a trade-off between risks versus benefits. The major issue is what to do about clots. The development and propagation of thrombus, as well as thromboembolic mechanism, is at the center of interventional therapy. For years, it was theorized that antithrombotic therapy with unfractionated heparin, an agent that binds with antithrombin III and interferes with the intrinsic coagulation pathway, would block thrombin formation and protect against the propagation of thrombus with a salutatory effect on ischemic stroke. Anecdotally, there was some support for efficacy, but scientific support was lacking.

One of the major challenges is to effectively determine whether or not an intervention is having an effect on outcome. The natural history of stroke is quite variable. Several neuroprotective trials demonstrated that a relatively minor stroke tends to have a good outcome, within a finite period of time, as part of the natural history. This finding can make it difficult to detect a positive effect of an intervention unless the effect is substantial. A major question is what constitutes a certifiable significant effect that potentially justifies approval by the Food and Drug Administration (FDA). Will a 20% difference between study intervention versus placebo suffice? The magnitude will impact the choice of the patient population in terms of how the potential agent is being assessed. A higher-risk population is easier for the detection of an effect than a lower-risk population. Furthermore, the potential efficacy will very much impact on how the study will need to be powered to determine a possible effect. In other words, an agent that limits infarct size by 50% or greater, within a certain therapeutic time

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window, will need less study patients to demonstrate a positive effect on outcome than a drug that limits infarct size by 30%.

The concept of therapeutic window for efficacy versus detriment is extremely important in clinical decision making. There is a limited time for correction of circulatory compromise before the ischemic cascade<sup>1</sup> evolves into a danger zone for potential hemorrhagic conversion of the evolving infarct (**Fig. 1**). Furthermore, the concept of reperfusion injury<sup>2</sup> is very real because the restoration of the circulation to irreversibly infarcted tissue can promote expanded brain tissue injury as excitatory neurotoxins, including free oxygen radicals, have enhanced access to the infarct with subsequently enhanced infarction size.

Four major targets of therapeutic intervention in acute ischemic stroke are the (1) restoration of the circulation with a timeframe in which the restored perfusion has more of a salutatory effect than a detrimental effect; (2) interference of the ischemic cascade pathways, which is predicated on reversible versus irreversible interference; (3) lowering cerebral metabolic demand so that the susceptible brain tissue is protected against impaired perfusion; and (4) protection against recurrent ischemic events. Examples of reperfusion of an occlusive cerebrovascular event include thrombolytic therapy,<sup>3</sup> the potential for ultrasound to enhance thrombolysis<sup>4</sup> and angioplasty with stenting,<sup>5</sup> and mechanical embolectomy with devices, such as the Merci clot retrieval device<sup>6</sup> (Concentric Medical of Mountain View, CA, USA) and the Penumbra clot retrieval device<sup>7</sup> (Penumbra, Inc, Alameda, CA, USA). Several efforts have been made with neuroprotective agents to interfere with the generation of cerebral infarcted tissue.<sup>8</sup> However, to date, even with various near misses,<sup>9</sup> no agent has been found to improve outcome in a statistically significant fashion that would justify its release by the FDA.<sup>10</sup> Certain neuroprotective approaches are designed to reduce the metabolic need of brain tissue that is underperfused. The prototypical approach is hypothermia, which is well established as having potential in protecting the brain against anoxic/ischemic insults, such as during cardiac arrest.<sup>11</sup> However, there



**Fig. 1.** Hemorrhagic conversion of an acute middle artery distribution cerebral infarct on non-contrast CT brain scan with arrow identifying the associated hemorrhagic transformation.

have been various potential clinical barriers with hypothermia, and it is not yet ready for prime time in our present armamentarium for acute ischemic stroke.<sup>12</sup>

### MECHANISM OF ISCHEMIC INSULT

A major issue in stroke management is the determination of the presumptive mechanism of the cerebral ischemic insult. Naturally, vessel occlusion would be expected to be more amenable to thrombolytic therapy than a nonobstructed vessel. Cardio-embolic stroke implies clot formation in the heart that traverses into the cerebral circulation. Embolic occlusion of a cerebral artery would be expected to be especially responsive to therapy designed to break up a clot. On the other hand, in situ small vessel thrombosis, the most commonly cited mechanism of lacunar-type stroke, may be less amenable to thrombolysis. Artery-to-artery embolism is a commonly cited mechanism for ischemic stroke and can be related to carotid or aortic arch plaque formation. There is also the potential for hemodynamic compromise with vessel stenosis and this might be more relevant in vertebrobasilar ischemia.<sup>13</sup> This concept is important because carotid intervention, despite significant stenosis, is not necessarily going to be beneficial for patients with symptoms referable to the vertebrobasilar system.

Potential mechanisms of ischemic stroke are summarized in **Box 1**. It is important to recognize that a significant percentage of patients with ischemic stroke have a mechanism that cannot be readily determined.<sup>14</sup> This point is perhaps of greater importance for the so-called stroke in the young, which is attributed to stroke in patients who are 45 years of age or younger and have no ongoing, well-recognized risk factors for ischemic stroke. In such patients, more esoteric causes of stroke are often brought

#### Box 1

##### Potential mechanisms of ischemic stroke

1. Large-artery thrombotic
2. Small-artery thrombotic (lacunar-type)
3. Artery-to-artery embolism
4. Cardio-embolic
5. Cerebrovascular dissection
6. Cerebral vasculitis
7. Cerebral sinovenous thrombosis
8. Hematological occlusive process (eg, sickle cell disease, thrombocytosis, polycythemia)
9. Iatrogenic (eg, ENT procedures affecting the extracranial vasculature)
10. Septic embolism from infectious endocarditis
11. Sympathomimetic agent-induced vasospasm
12. Hypotensive with cerebral hypoperfusion (eg, watershed infarction)
13. Secondary cerebral ischemia following aneurysmal rupture
14. Noninflammatory cerebral vasculopathy (eg, moyamoya disease)
15. Hypercoagulability (eg, antiphospholipid syndrome; antithrombin III, protein S, or protein C deficiency; malignancy related)
16. Nonseptic embolism from marantic endocarditis

into the differential diagnosis (**Box 2**), such as vascular dissection, migraine, hypercoagulable state, vasculitis, oral contraceptive use in women, and paradoxical cerebral embolism.<sup>15</sup>

The determination of the stroke mechanism helps in terms of diagnostic yield for investigational studies. Naturally, the history of standard cardiac disease–related risk factors, including advanced age, hypertension, hyperlipidemia, and diabetes mellitus, will more likely identify a cardiogenic mechanism than in an individual aged 45 years or younger without these risk factors. In such a circumstance, mechanisms, such as paradoxical cerebral embolism, through a patent foramen ovale, atrial myxoma, and endocarditis will be of potentially higher yield diagnostically than in a 70-year-old patient with long-standing hypertension and hyperlipidemia with a history of myocardial infarction. In our evolving health care system, whereby diagnostic study choice might be dictated by the expected yield frequency, we may be faced with paradigms that mandate risk stratification from the start. Presently, we have available a virtual cornucopia of diagnostic studies in acute ischemic stroke that seems to increasingly expand, especially when we start to factor in genetic studies. However, cost issues raise the important question of how such studies will impact patient management to justify cost.

## GENERAL PRINCIPLES OF ISCHEMIC STROKE MANAGEMENT

The ABCs of resuscitation for acute ischemic stroke must be attended to, especially in patients with moderate to severe infarction of the cerebral hemispheres, the brainstem, or the cerebellum. The airway may be compromised by pharyngeal muscle dysfunction, and loss of control of the oropharyngeal secretions increases the risk for aspiration. Most patients do not require supplemental oxygen to keep normal oxygen saturations. Respiratory compromise will mandate ventilator support. Noninvasive positive-pressure ventilator support may suffice but, if patients are at a high risk for aspiration, this option is contraindicated. Unfortunately, the requirement for

### Box 2

#### Differential diagnosis of ischemic stroke in the young

1. Paradoxical cerebral embolism via patent foramen ovale
2. Migrainous infarction
3. Oral contraceptive with resultant hypercoagulopathy
4. Infectious endocarditis
5. Connective tissue disorder
6. Cerebrovascular dissection
7. Moyamoya disease
8. Cocaine-induced vasculitis
9. Anticlotting deficiency
10. Sinovenous thrombosis
11. Sickle cell disease
12. Polycythemia vera
13. Thrombocytosis
14. Meningovascular syphilis

endotracheal intubation is associated with a high 30-day mortality rate after ischemic stroke.

Neurological checks and vital signs are typically ordered every 4 hours in patients with moderate to large infarcts, with closer monitoring after thrombolytic therapy in an intensive care unit as well as for those patients who are neurologically unstable. For patients receiving recombinant tissue plasminogen activator (rt-PA), the blood pressure should be measured every 15 minutes for 2 hours after the initiation of the infusion, then every 30 minutes for 6 hours, and then every 60 minutes until 24 hours after the initiation of treatment.

Patients seen on an emergency basis with symptoms of stroke need an immediate complete blood count (CBC), platelet count, prothrombin time/international normalization ratio (INR), partial thromboplastin time, and metabolic studies to assess for significant hypoglycemia or hyperglycemia, as well as a noncontrast computed tomography (CT) brain scan and electrocardiogram (EKG). In certain medical centers, the magnetic resonance imaging (MRI) brain scan will be substituted for the CT brain scan as long as imaging sequences are available that can reliably distinguish an ischemic insult from a hemorrhagic one. It is common to see an imaging protocol, at certain centers, that attempts to compare perfusion with diffusion imaging, looking for the so-called mismatch between perfusion and diffusion lesion supportive of reversibly impaired tissue often termed the ischemic penumbra.<sup>16</sup> Such imaging assessment of salvageable brain tissue has been reported to be of value with both MR<sup>17</sup> as well as perfusion CT scan techniques.<sup>18</sup> In addition, incorporation of such potential mismatch assessment, with either MR or CT techniques, along with vessel imaging which can include, respectively, magnetic resonance angiography (MRA) or CT angiography (CTA) (**Fig. 2**). Alternatively, transcranial Doppler ultrasonography (TCD) can be used in the emergency department setting to assess for vessel patency



**Fig. 2.** CT angiogram that demonstrates (*top*) total middle cerebral artery occlusion ipsilateral to (*bottom*) high-grade internal carotid artery origin stenosis.

in a noninvasive fashion.<sup>19</sup> However, studies that delay the administration of thrombolytic therapy are counterproductive. Certain readily available imaging findings, such as the hyperdense middle cerebral artery on CT brain scan, reflective of a presence of a clot may have an impact on the response to therapy.<sup>20</sup>

Appropriate monitoring is important in terms of protection of the airway, and protection against aspiration, as well as the monitoring of effective breathing, with pulse oximetry and adequate circulation with the assessment of an adequate mean arterial pressure, for the clinical situation. Respiratory compromise will mandate ventilator support, if necessary, although noninvasive respiratory support has its potential advantages as long as aspiration risk does not contraindicate this option. In this regard, a swallowing study becomes mandatory for any patient with clinically significant neurologic deficits in acute ischemic stroke. Cardiac monitoring can be of particular value if there is evidence of cardiac ischemia associated with the stroke or risk of cardiac arrhythmia that may impact management, such as paroxysmal atrial fibrillation. This arrhythmia is reported to be present in up to 9.2% of patients with definite ischemic stroke or transient ischemic attack.<sup>21</sup> The yield of finding this potential cardio-embolic source correlates with the diligence with which it is sought and might well require Holter monitoring up to day 7 of the time of presentation of the arrhythmia.<sup>22</sup> Stroke units are particularly well suited for such monitoring of patients with acute ischemic stroke and are clearly established to improve outcome. Blood pressure monitoring, mentioned previously, is important not only from the standpoint of protection against unacceptable elevation following thrombolytic therapy but also in terms of avoiding relative hypotension, which can, at least theoretically, lead to extension of the infarction. Stroke units are particularly well suited for such monitoring of the patients' neurologic and hemodynamic status and have clearly been demonstrated to have a positive impact on outcome.

Optimal blood sugar management is still under investigation in acute ischemic stroke. It is generally thought that hyperglycemia contributes to adverse outcomes.<sup>23</sup> However, use of an insulin sliding scale, as opposed to continuous insulin infusion, may not be the optimal approach.<sup>24</sup> It is generally accepted that dextrose-containing intravenous fluids should be avoided in the acute stroke setting. There is also evidence that persistent body temperature elevation has an adverse effect on stroke outcome and this should be avoided.<sup>25</sup> Patients with ischemic stroke are often volume depleted. In such circumstances, the administration of intravenous normal saline at 1 to 2 mL/kg/h is advantageous to maintain fluid balance. In addition, the electrolyte magnesium serves to block the excitatory glutamate receptor, which has led to a recommendation for the normalization of the serum magnesium when deficient.

Blood pressure control in acute ischemic stroke is presently viewed as permissive in terms of acceptable ballpark values of a systolic blood pressure of  $180 \pm 20$  mm Hg and a diastolic blood pressure of  $110 \pm 10$  mm Hg. This approach is primarily based on the theoretical concerns over too aggressive blood pressure control promoting hypoperfusion in the setting of the disruption of cerebral autoregulation.<sup>26</sup> Such hypoperfusion, in turn, promote the extension of the infarct and worsen outcomes. The natural corollary of this is that hypertensive therapy might have a potential benefit in protecting susceptible brain tissue in the region of the infarct (ie, the penumbra). However, such an approach, despite the theoretical attractiveness, has not been clearly established as beneficial.<sup>27</sup> From a practical standpoint, it is advisable to avoid antihypertensive agents, with markedly elevated blood pressure, that can cause a precipitous drop in blood pressure with the potential for cerebral hypoperfusion. Agents that have been specifically cited for such blood pressure management include

labetalol and nicardipine. Labetalol boluses result in mild and fairly predictable decreases in blood pressure, and nicardipine can be rapidly titrated for a target blood pressure with little effect on heart rate or cerebral vasoreactivity. On the other hand, agents, such as nifedipine or clonidine, are best avoided. In the malignant intractable elevation of the blood pressure, the agent sodium nitroprusside may still have a place in management as long as an arterial line is available for accurate monitoring of the antihypertensive effect and intracranial hypertension is not suspected. It is important to keep in mind that blood pressure guidelines with the use of an agent, such as rt-PA, are systolic blood pressure less than or equal to 185 mm Hg and diastolic blood pressure less than or equal to 110 mm Hg. Therefore, with the use of such a thrombolytic agent, labetalol, nicardipine, or the nitroglycerin patch are attractive choices.

As long as there are not concerns about aspiration, enteral nutrition is preferred over parenteral alimentation. Over the longer term, if aspiration remains a concern, then the percutaneous enteral gastrostomy tube becomes indicated. Elevation of the head to roughly 30° can protect against aspiration, although flat positioning of the head may improve blood flow velocity in the acute setting.<sup>28</sup> Proper nutrition is an important means to promote recovery after stroke and needs to be instituted as soon as feasible.

Prevention of deep venous thrombosis (DVT), and the subsequent concern about pulmonary embolism, is of the utmost importance in acute ischemic stroke. It is well established that subcutaneous heparin or heparinoid is indicated for DVT prophylaxis in acute ischemic stroke and is part of the guidelines of both the American Academy of Neurology and the American Stroke Association<sup>29</sup> for acute ischemic stroke management. Naturally, the risk of DVT is reflective of immobility and the longer patients are immobile, the greater the likelihood of complications of immobility, such as DVT, pressure sores of the skin, and infections related to a prolonged recumbent posture. Unfractionated heparin, with a dosage of 5000 units subcutaneous twice a day, is the most cost-effective but may not have the efficacy of low-molecular-weight heparins, such as enoxaparin.<sup>30</sup> Intermittent pressure stockings can also be advantageous in such a clinical setting, especially if the use of heparin or heparinoid is contraindicated for reasons, such as heparin-induced thrombocytopenia.<sup>31</sup> Every effort should be made to mobilize patients with acute stroke as early as possible in an enhanced effort to protect against such potential problems with prolonged immobility.

It is well recognized that part of the early mobilization effort includes rehabilitative specialists to assess various functional limitations and determine how best to address these limitations when they are present. The assessment of swallowing function, often with the input of a speech pathologist, is vitally important to protect against aspiration pneumonia in patients who have had a stroke who are susceptible to such aspiration. This risk is usually associated with either larger hemispheric infarcts, which impact on the level of alertness, or infarcts involving the brainstem or cerebellum, which impair bulbar function with secondary dysphagia. Speech therapists also help in assessing and promoting the recovery of associated communication deficits both in terms of aphasia and dysarthria. Occupational and physical therapists work in tandem in the assessment and therapeutic intervention for motor, coordination, and gait deficits that may be associated with the acute ischemic stroke. Multidisciplinary rounds in stroke units can be beneficial for the coordination of various services in an effort to promote optimal recovery for the stroke victim. This includes the potential neuropsychological assessment when cognitive deficits interfere with the neurorehabilitative process. Denial, neglect, and resistance to the rehabilitative specialists, not uncommonly seen with nondominant hemispheric infarcts, can be quite counterproductive to the therapists' efforts. It is also important to screen for depression, which is commonly encountered in patients who have had a stroke. Significant depression,

with the tendency toward social withdrawal associated with it, can impede the level of cooperation expected of patients in the neurorehabilitative process. Selective serotonin reuptake inhibitors, such as fluoxetine, have been reported to improved depressed mood in acute stroke<sup>32</sup> and may also help in the recovery of motor function.<sup>33</sup> **Box 3** summarizes general principles in the assessment and management of acute ischemic stroke.

### THROMBOLYTIC THERAPY

A major advance in improving acute ischemic stroke outcome has been the demonstration that certain agents have the potential to disrupt a clot obstructing a cerebral vessel. It clearly makes theoretical sense that the restoration of impaired cerebral blood flow should help ischemic stroke outcomes *if* it can be done in a timely fashion. Demonstration of efficacy in thrombolytic therapy was not an overnight event, however. Initial attempts at clot lysis, with an agent such as streptokinase,<sup>34</sup> were not only not helpful but potentially harmful. However, there was scientific support for such an approach with various laboratory models of ischemic stroke as well as the obvious impetus from several cardiac interventional trials.

#### Box 3

##### Basic assessment and management measures in acute ischemic stroke

1. Assess vital signs to ensure adequate breathing, regularity of pulse, presence or absence of fever, and blood pressure range that is appropriate for the clinical presentation
2. Protection against elevated body temperature with an agent, such as acetaminophen
3. Avoidance of hyperglycemia and hypoglycemia; generally, dextrose-containing intravenous fluids are avoided
4. Stat (immediate) noncontrast CT brain scan with option of diffusion/perfusion-weighted MRI with gradient echo at certain centers; protocols at certain centers may include perfusion CT brain scan with CTA or MRA
5. Stat blood work, including CBC, prothrombin time/INR, partial thromboplastin time and metabolic profile
6. EKG to assess for cardiac arrhythmia, such as atrial fibrillation, as well as for acute myocardial ischemia
7. Determination of the appropriateness of possible interventional therapy, such as thrombolytic therapy, clot retrieval, mechanical disruption, or angioplasty with stenting
8. Assessment of swallowing capacity in an effort to avoid aspiration
9. DVT prophylaxis
10. Early mobilization to protect against potential complications of immobility, such as skin breakdown, DVT, and infections
11. Heart rhythm monitoring
12. Further assessment of stroke mechanism, which might include carotid/vertebral duplex scan, cerebral angiography, transcranial Doppler ultrasound, lipid profile, platelet function studies, assessment for a hypercoagulable state, 2-dimensional or transesophageal echocardiography, evaluation for a connective tissue disorder, sickle cell preparation, blood cultures, syphilis serology
13. Initiation of aspirin at 160 to 325 mg/d if no contraindication
14. Rehabilitation services consultation, which can include speech therapy, occupational therapy, and physical therapy as appropriate

Rt-PA was released by the FDA in the United States for the treatment of acute ischemic stroke in 1996. This release was based on the National Institutes of Neurologic Diseases and Stroke (NINDS) trial,<sup>35</sup> which demonstrated roughly a 30% improvement in the rate of essentially full recovery from stroke at 3 months compared with placebo. The 6.4% risk of symptomatic brain hemorrhage associated with rt-PA has tempered enthusiasm along with the indications for its use (**Box 4**) and the contraindications for its use (**Box 5**). Despite initial concerns about just how effective thrombolytic therapy is as opposed to concerns about bleeding risk, cumulative information from ongoing studies has convincingly demonstrated its efficacy and justified its use.<sup>36</sup> Concern about the risk of brain hemorrhage remains with rt-PA, and this risk tends to be enhanced in patients with larger infarcts with a National Institutes of Health (NIH) Stroke Scale greater than 22, those with an early infarction pattern on CT brain scan that involves more than one-third of the middle cerebral artery territory and those of advanced age with an increased risk of underlying cerebral amyloid angiopathy.

Challenges related to the 3-hour time window for the availability of intravenous infusion has led to no more than 5% of patients with acute ischemic stroke receiving this agent.<sup>37</sup> However, this percentage can clearly be improved in sophisticated centers that are geared to reduction in the door-to-needle time for the administration of this agent.

The dose of rt-PA is 0.9 mg/kg up to a maximum of 90 mg, with 10% given by intravenous bolus over 1 minute and the remainder infused over 1 hour. The patient is generally carefully monitored in an intensive-care-unit setting for at least the first 48 hours, and a follow-up CT brain scan is obtained at 24 hours to assess for possible subclinical hemorrhagic transformation of the infarct and to allow guidance in terms of initiation of antiplatelet or anticoagulant therapy, which needs to be held for at least 24 hours after the rt-PA infusion. Naturally, clinical evidence of intracerebral hemorrhage, based on neurologic worsening, mandates an immediate CT brain scan. The demonstration of intracerebral hemorrhage leads to efforts to limit the amount of bleeding with 6 to 8 units of cryoprecipitate or fresh frozen plasma and 10 units of single-donor platelets. Neurosurgical consultation is also recommended in case there is a potential benefit from hematoma evacuation. An additional concern with rt-PA is the risk of orolingual angioedema, which is enhanced in patients receiving angiotensin-converting enzyme inhibitors. This condition has the potential to

**Box 4****Indications for the use of recombinant intravenous tissue plasminogen activator in acute ischemic stroke**

1. Presentation, evaluation, and treatment within 3.0 to 4.5 hours
2. Finite neurologic deficit on neurologic examination as assessed by the NIH Stroke Scale with the absence of spontaneous significant resolution during initial evaluation
3. Noncontrast CT brain scan, or alternative MRI at certain centers, that is compatible with an acute ischemic stroke
4. Lack of an alternative explanation for the neurologic presentation, such as severe hypoglycemia or hyperglycemia or the residua of a focal seizure (ie, Todd paralysis)
5. Effort to address potential risks versus benefits of this agent with patients and close family members, which is documented in the records and with some centers requesting an effort at an informed consent form; informed consent is presumably most appropriate, at this time, for use of this agent beyond the standard 3-hour therapeutic window
6. Persistent neurologic deficit that is not rapidly resolving during the evaluation process

**Box 5****Contraindications to the use of intravenous rt-PA in acute ischemic stroke**

1. Clinical or imaging evidence of intracerebral or subarachnoid hemorrhage
2. Intracranial or intraspinal surgery within 3 months of presentation
3. Prior ischemic stroke within 3 months of presentation
4. Serious head trauma within 3 months of presentation
5. History of intracranial hemorrhage
6. Persistently uncontrolled high blood pressure at the time of presentation with systolic blood pressure greater than 185 mm Hg or diastolic blood pressure greater than 110 mm Hg; agents, such as intravenous labetalol or nicardipine and nitroglycerin paste, may be considered for the maintenance of adequately controlled blood pressure, with recognition that the blood pressure may fluctuate to a significant degree in the acute stroke setting
7. Seizure at the onset of the stroke that is thought to likely explain the deficit at the time of presentation
8. Active internal bleeding
9. Evidence of intracranial neoplasm, arteriovenous malformation, or cerebral aneurysm
10. Acute myocardial infarction within the previous 3 months<sup>a</sup>
11. Bleeding abnormality, which can include warfarin therapy with an INR greater than 1.7 or a prothrombin time greater than 15 seconds, use of heparin within 48 hours of presentation with a significantly prolonged activated partial thromboplastin time at the time of presentation, or a platelet count less than 100,000/mm<sup>3b</sup>
12. For the 3.0- to 4.5-hour window: aged 80 years or older, prior ischemic stroke with diabetes mellitus, and any recent use of an oral anticoagulant

<sup>a</sup> Initially viewed as an absolute contraindication, but now viewed, at least by some, as a relative contraindication dependent on the risk of transmural rupture.

<sup>b</sup> The release of the agent dabigatran for stroke prevention in atrial fibrillation has necessitated avoiding within 48 hours of dosing, with a normal activated partial thromboplastin time (aPTT), as a guideline.

compromise the airway, and there have been reports of response to antihistamine agents along with steroid therapy.

The sooner patients receive the rt-TPA, the greater the likelihood of a positive response. In a report of cumulative experience with this agent,<sup>38</sup> the odds ratio (OR) of an excellent outcome, compared with placebo, is 2.8 for patients treated within 90 minutes, 1.6 for patients treated within 91 to 180 minutes, 1.4 for patients treated at 181 to 270 minutes, and 1.2 for patients treated within 271 to 360 minutes. Patients most likely to benefit are reported to be those with milder neurologic deficit, absence of diabetes mellitus and normal blood glucose, normal CT brain scan, and normal blood pressure.<sup>39</sup> Despite this, it seems that the quicker recanalization is effectively achieved, the more likely is one to see an improved outcome with revascularization procedures.<sup>40</sup>

The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial<sup>41</sup> did not find that potential benefits of extending the administration of rt-PA to a 3- to 5-hour window was associated with improvement that would justify the increased risk of cerebral hemorrhage. It was speculated that a mismatch between clinical deficit and diffusion-weighted imaging (DWI) MRI might identify patients more likely to benefit from rt-PA in the 3- to 6-hour therapeutic window. However, such a therapeutic approach did not translate into improved outcomes or enhanced reperfusion.<sup>42</sup> Despite these discouraging results for the extension of the therapeutic

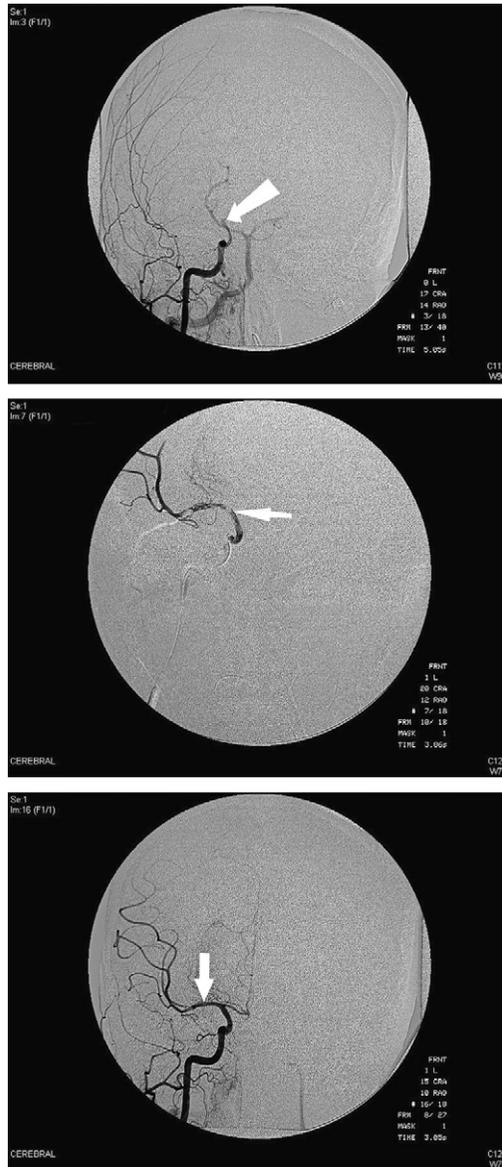
window for rt-PA, Hacke and colleagues,<sup>43</sup> for the European Cooperative Acute Stroke Study (ECASS) investigators, reported a 52.4% favorable outcome with rt-PA compared with 45.2% with placebo (OR = 1.34,  $P = .04$ ). It is important to note that this study excluded patients aged more than 80 years, those with a combination of previous stroke and diabetes mellitus, and those on oral anticoagulant therapy even if the INR was in the nontherapeutic range. The risk of cerebral hemorrhage was 27.0% with rt-PA compared with 17.6% for placebo, but symptomatic hemorrhage, respectively, was 2.4% vs 0.2%,  $P = .008$ ). Furthermore, the mortality rate was not statistically significantly different (7.7% vs 8.4%).

In the scientific advisory from the American Heart Association/American Stroke Association,<sup>44</sup> which recommended an extended window of rt-PA to 4.5 hours based on this ECASS study, symptomatic cerebral hemorrhage was interpreted as being 7.9%, by NINDS study criteria, with rt-PA compared with 3.5% with placebo (OR = 2.38,  $P = .0008$ ). To date, the FDA has not approved the extension of the window to 4.5 hours, which creates a dilemma for the clinician treating acute ischemic stroke. In such a circumstance, if one is convinced that intravenous rt-PA is a legitimate option with a 3.0- to 4.5-hour window, then an informed consent should probably be developed and approved by the medical center administration whereby patients and family members are made aware that there is scientific support for the use of such an agent with an extended window, but that the evidence, to date, has not resulted in approval by the FDA.

Intra-arterial thrombolytic therapy is an exciting option for acute ischemic stroke for patients who are beyond the therapeutic window for intravenous rt-PA and at centers that have special expertise in the use of such therapy. However, the time window for therapeutic benefit versus enhanced risk of hemorrhagic complication is still being worked out. Efforts have been made to combine intravenous rt-PA with intra-arterial rt-PA, the so-called bridging therapy.<sup>45</sup>

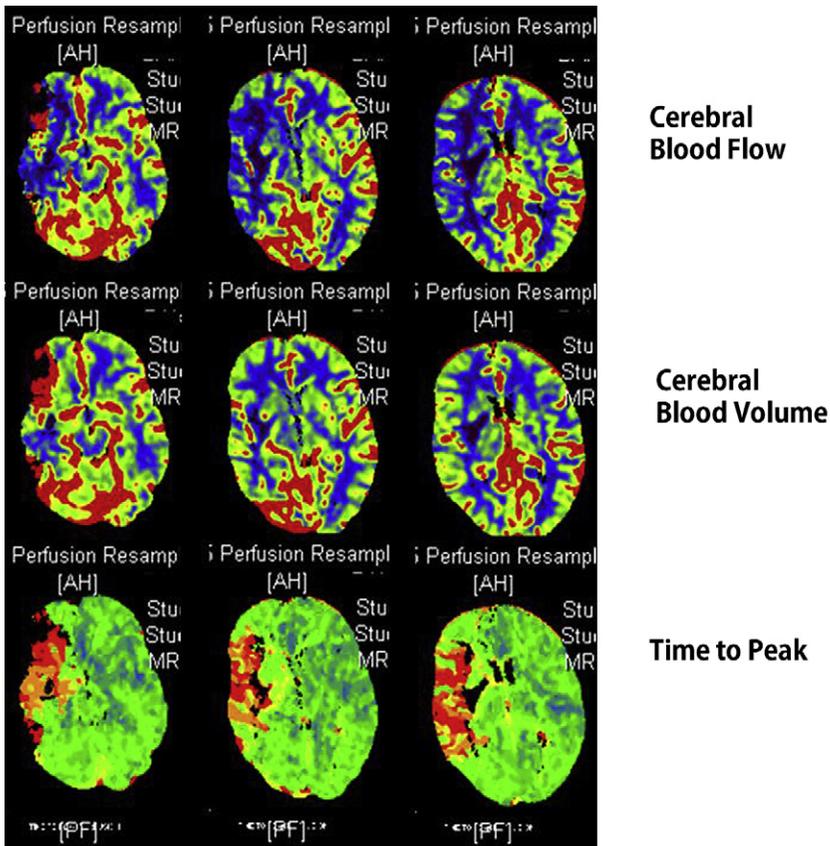
This therapy theoretically allows immediate access to intravenous therapy but is in recognition that the recanalization success with this approach can be improved on. A recent study reported an acute recanalization rate with intravenous rt-PA of only 21.25%.<sup>46</sup> The use of intra-arterial thrombolysis has been reported to have a recanalization rate substantially greater than intravenous therapy.<sup>47</sup> Unfortunately, the bridging trial reported by Lewandowski and colleagues,<sup>48</sup> consisting of 0.6 mg/kg intravenous rt-PA with 10% by bolus and the remainder over 30 minutes, at a maximum dose of 60 mg, followed by intra-arterial rt-PA administered to the clot within 2 hours of the intravenous dose, with a maximum dose of 20 mg, reported a treatment mortality of 29%. This finding was in distinction from 5.5% in the comparison group that only received the intra-arterial rt-PA ( $P = .06$ ). Despite this sobering endpoint, the researchers made note of the 54% successful recanalization rate versus 10% ( $P = .03$ ) as well as the improved NIHSS scores in survivors at 3 months out. This finding has led to the Interventional Management of Stroke (IMS) trial, which has progressed to a pivotal IMS-III study in progress.<sup>47</sup> Preliminary data suggests an acceptable safety profile and improved outcomes compared with historical controls from the NINDS trial.<sup>34</sup> An example of successful recanalization is demonstrated in **Fig. 3**.

Most patients with acute ischemic stroke are not eligible for intravenous rt-PA because of the time-window limitations. However, imaging studies have suggested that perfusion-diffusion mismatch<sup>17</sup> (ie, relative sparing of perfusion adjacent to the area of completed infarction demonstrating tissue at risk) (**Fig. 4**) may allow the identification of patients beyond the 3-hour, or 4.5-hour, window of opportunity who still may benefit from thrombolytic therapy. Such potential efficacy beyond the standard time window, with the use of intra-arterial thrombolytic therapy alone, was supported



**Fig. 3.** Distal right internal carotid artery near occlusion (*top*) with successful reconstitution of right middle cerebral artery flow (*middle*) along with anterior cerebral artery flow (*bottom*) with intra-arterial thrombolytic therapy (*arrows*).

by the Prolyse in Acute Cerebral Thromboembolism (PROACT) study.<sup>49,50</sup> These studies (PROACT-I and -II) looked at the recanalization rate of intra-arterial recombinant prourokinase as a function of safety and outcome in acute ischemic stroke with a 6-hour therapeutic window. Both groups received intravenous heparin as part of the study protocol, with the control group receiving heparin alone. The recanalization rate was 66% in the study group compared with 18% in the control group



**Fig. 4.** CT cerebral blood flow versus blood volume perfusion imaging, which demonstrates a large mismatch that reflects susceptible versus infarcted tissue as demonstrated in the time-to-peak image.

( $P < .001$ ), and with good outcome at 90 days, 40% in the study group compared with 25% in the control group (OR = 2.13,  $P = .04$ ). However, the 10% risk of intracerebral hemorrhage in the study group, compared with 2% in the control group ( $P = .06$ ), translated into this thrombolytic agent never being approved by the FDA for such an indication. Despite this, the most recent Guidelines for the Management of Adults with Ischemic Stroke from the American Stroke Association Stroke Council<sup>26</sup> list intra-arterial thrombolysis as a therapeutic option for patients treated within 6 hours of a major stroke associated with middle cerebral artery occlusion and who have access to a facility with acceptable expertise in the interventional realm for such a procedure.

The challenge of the consequences of symptomatic severe occlusive vertebrobasilar disease has led several qualified centers to extend the therapeutic window for intra-arterial thrombolytic therapy to up to 24 hours. This extension is based on the natural history of severe brainstem stroke in terms of the cumulative severe morbidity and mortality, which is 90% or greater, whereas successful revascularization has the potential to make a significant improvement in outcome.<sup>51</sup> There are several presentations and anecdotal reports of great saves in terms of patients who seemed to be headed

toward an irretrievable locked-in state who recovered remarkably well with such therapy. Generally, these are patients who are beyond the 3-hour window for intravenous rt-PA based on the time involved in determining the degree of vascular involvement with neurovascular imaging. However, faster determination of the occlusive process with noninvasive imaging techniques, such as CTA, may expedite the detection and potential for intervention in severe vertebrobasilar occlusive disease.<sup>52</sup> However, a recent study reported that contrast-enhanced MRA was the most sensitive noninvasive test for vertebral artery stenosis when compared with CTA and ultrasound.<sup>53</sup>

Montavont and colleagues<sup>54</sup> looked at 18 consecutive patients with vertebrobasilar ischemia who were treated with intravenous rt-PA within 7 hours of presentation. At 3 months, they reported that 10 patients were independent, with a modified Rankin Scale of 0 to 2, whereas 8 had a poor outcome with a modified Rankin Scale of 3 to 6. In a systematic analysis of intra-arterial versus intravenous thrombolytic therapy for basilar artery occlusion,<sup>55</sup> Lindsberg and Mattle reported that recanalization was more frequent with intra-arterial versus intravenous therapy (65% vs 53%,  $P = .05$ ), with similar frequency of good outcomes in both groups (24% vs 22%). However, only 2% of those patients who failed to recanalize had a good outcome. The Basilar Artery International Cooperation Study (BASICS) looked at the treatment and outcomes in acute basilar artery occlusion.<sup>56</sup> There were 619 patients in this registry and 27 were excluded because they did not receive either antithrombotic therapy alone, intravenous therapy, or intra-arterial thrombolysis, and all had a poor outcome. For those who received some form of therapy, 68% had a poor outcome, and no statistically significant superiority was found for any of the 3 treatment arms. This finding underscores the expected poor prognosis in acute basilar artery thrombosis even with thrombolytic therapy.

In summary, there is now an established 3-hour window for the use of intravenous rt-PA for patients who fulfill the criteria, assuming that they and their loved ones are in agreement with receiving this agent with the recognition of its relatively small, but real, risk of serious hemorrhagic complications. This established window is viewed as a standard of care, and there are potential medicolegal ramifications for its use, or nonuse, with most of these ramifications related to failure to use this agent for patients who were eligible to receive it. The extension of the therapeutic window for rt-PA to up to 4.5 hours is potentially exciting, with an endorsement by the Stroke Council of the American Stroke Association, but there is also a lack of approval for this extended window by the FDA. It is advisable, at this time, to seriously consider it as an option for a person who qualifies for the extended window, with the availability of an informed consent to clearly spell what seem to be less of a benefit/risk ratio compared with the 3-hour window. The availability of extended windows for thrombolytic therapy, particularly in reference to intra-arterial rt-PA, should be predicated on the experience and critical mass of the particular stroke center to avoid what could be interpreted as a haphazard window of availability depending on the coverage at the particular center at any one time. Because of the lack of definitive controlled trials of the extended window with either intravenous/intra-arterial rt-PA bridging or intra-arterial rt-PA alone, and without FDA approval for such an indication, it is expected that a protocol will be in place for a particular medical center that is approved by that institution's human subjects committee along with an informed consent.

## CLOT-RETRIEVAL/ANGIOPLASTIC DEVICES

There are now 2 FDA-approved clot-retrieval devices available for patients with acute ischemic stroke: the Merci clot-retrieval device<sup>6,57-59</sup> and the Penumbra clot-retrieval

device.<sup>7,60</sup> Their release by the FDA was based on their demonstrated ability to extract a clot within the intracerebral circulation and restore blood flow through that particular involved vessel. Their impact on outcome in acute ischemic stroke has been favorable, with the caveat that such an interventional procedure is operator dependent and reflects the skill and experience of a particular interventionalist. The therapeutic window is generally viewed within 3 to 8 hours of presentation, taking into account the accepted first choice of intravenous rt-PA for patients presenting within the 3-hour window who do not have contraindications to its use.

In the Mechanical Embolus Removal in Cerebral Ischemia (MERCi) trial,<sup>6</sup> with a mean procedural time of 2.1 hours, with a 3- to 8-hour therapeutic window, the recanalization rate was 48% for patients with documented occlusions of either the middle cerebral artery, terminal internal carotid artery, or the basilar artery. This finding was compared with the reported 18% in the PROACT-II historical control arm ( $P < .0001$ ).<sup>50</sup> For patients in the MERCi trial who did not have good recanalization, adjuvant intra-arterial rt-PA was available with or without angioplastic intervention. The significant periprocedural complication rate was 7.1%, and intracerebral hemorrhage was observed in 7.8%. Of particular note, from an outcome standpoint, good neurologic recovery was seen in 46% of those patients who were successfully recanalized but in only 10% of those who did not recanalize ( $P < .0001$ ).

In the Multi MERCi trial, the newer-generation embolus-retrieval device was tested in patients with persistent large vessel clot despite intravenous rt-PA.<sup>57</sup> This test was compared with a recanalization rate of approximately 48% and an enhanced rate of up to 60% when combined with intra-arterial thrombolytic agents. The results provide caution about the potential benefits versus risks of such intervention, however. Despite a recanalization rate of 57.3% with this device, along with 69.5% when combined with thrombolytic therapy, favorable outcome was 36% clinically and the mortality rate was a worrisome 34%, whereas the symptomatic intracerebral hemorrhage rate was 9.8%. The investigators noted that clinical outcome was reflective of the recanalization rate, which was also emphasized in the pooled analysis of the MERCi and Multi MERCi trials,<sup>58</sup> and this pooled analysis also reported greater success with second-division middle cerebral artery occlusions than with trunk occlusions.<sup>59</sup>

The Penumbra device, consisting of a reperfusion catheter and separator with or without a thrombus removal ring, was reported to have a recanalization rate of 100% in one international study of 20.<sup>60</sup> Kulcsar and colleagues<sup>61</sup> reported their experience with this device in 27 consecutive patients. They observed a recanalization rate of 93%, no symptomatic intracerebral hemorrhages, significant clinical improvement in roughly 50%, and an all-cause 3-month mortality of 11%. The mean time to initial angiographic imaging was 4 hours and 26 minutes in this study, and the mean time to attain revascularization was an additional 97 minutes in a patient population who had presented within 3 hours of their stroke onset.

In addition to the Multi MERCi and Penumbra, there are various alternatives involving either microwire or microcatheter clot disruption, which may also include the incorporation of angioplasty once the reestablishment of vessel patency has been achieved. In a study by Noser and colleagues,<sup>62</sup> clot maceration with microcatheter/microwire was followed by either angioplasty, stent, or snare in 32 patients who also received adjuvant thrombolytic therapy. They reported a favorable outcome in 59% and a mortality rate of 12.5%. Somewhat more sobering was a report of balloon angioplasty with or without snare, in addition to either intravenous or intra-arterial thrombolytic therapy.<sup>63</sup> Although the recanalization rate was impressive at 86%, the mortality rate was 53%.

In summary, clot-retrieval devices are now available at up to an 8-hour therapeutic window of intervention and addition to refinements in microwire/microcatheter clot maceration as well as angioplasty with or without snare endovascular interventions. This evolution of what has been termed aggressive mechanical clot disruption requires special expertise in terms of the application of such procedures in the acute ischemic stroke setting. Various devices have been FDA approved, based on their potential success in recanalization, which is clearly correlated with improved outcome, although the review process for such device approval has caused some consternation among stroke specialists.<sup>64</sup> As of the present time, one can draw their own conclusions about the choice of procedure based on the data at hand. However, one must also factor in the delicacy of such intervention, with reported results most assuredly reflective of procedural skills and experience.

### **ASPIRIN IN ACUTE ISCHEMIC STROKE**

Two studies have demonstrated modest improvement in outcome with aspirin therapy in acute ischemic stroke. Naturally, this assumes that patients are tolerant of aspirin and that there is no contraindication, such as the withholding of both antiplatelet and anticoagulant therapy for at least 24 hours after the administration of rt-PA. The International Stroke Trial (IST) Collaborative Group looked at 330 mg of aspirin administered within the first 48 hours of an acute ischemic stroke,<sup>65</sup> whereas the Chinese Acute Stroke Trial (CAST) looked at a dose of 160 mg of aspirin.<sup>66</sup> Pooled data of the 40,000 patients entered in the 2 trials reported a 1.6% versus 2.3% reduced risk of recurrent stroke with aspirin, although the risk of hemorrhagic stroke was a bit higher at 1.0% versus 0.8%.<sup>67</sup>

There has been some interest in clopidogrel loading in acute ischemic stroke in an effort to protect against the extension of the infarction and progression of the neurologic deficit. This approach has been extrapolated from cardiac studies, which have suggested that higher-dose clopidogrel (600 mg vs 300 mg) in acute ST-segment elevation myocardial infarction is beneficial.<sup>68</sup> However, as with many antiplatelet studies, there are conflicting reports; the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS 7) investigators<sup>69</sup> reported no difference between double-dose versus standard-dose clopidogrel or aspirin in acute coronary syndromes.

### **ANTICOAGULANT THERAPY IN ACUTE ISCHEMIC STROKE**

Anticoagulant therapy in acute ischemic stroke was, for years, a commonly used therapeutic regimen in an effort to promote dissolution of thrombus formation or propagation of the thrombus, which was viewed as a common mechanism of stroke-in-evolution. However, the IST report<sup>65</sup> was one of several studies that have led to the recommendation that the only clear indication for anticoagulant therapy in the acute ischemic stroke setting is for DVT prophylaxis.<sup>26</sup> In IST, for example, subcutaneous heparin, at 5000 or 12,500 IU twice a day, was not found to be beneficial in acute ischemic stroke, although most clinicians recognize the value of lower-dose anticoagulant therapy in patients who have had a stroke with limited mobility for the protection against DVT and risk of pulmonary embolism. A pivotal trial that led to a rethinking of full-dose anticoagulants in acute ischemic stroke was the Trial of ORG 10,172 in Acute Stroke Treatment (TOAST).<sup>70</sup> This study of the low-molecular-weight heparinoid danaparoid reported no significant improvement in acute ischemic stroke outcome at 3 months, although there was an apparent positive response at 7 days.

Bath and colleagues<sup>71</sup> published a meta-analysis of randomized controlled trials of low-molecular-weight heparins and heparinoids in acute ischemic stroke and concluded that any potential benefit in the reduction of venous thromboembolic events was negated by an increased risk of extracranial bleeding. Perhaps even more sobering was the report that low-molecular-weight heparin was not superior to aspirin in patients with acute ischemic stroke in terms of functional outcome at 2 weeks or 3 months.<sup>72</sup> The investigators could not exclude some potential benefit. However, agents, such as activated factor X inhibitor idraparinux, apparently may produce more harm than any potential good.<sup>73</sup> On the other hand, there is clearly support for the efficacy of anticoagulant therapy in the protection against ischemic stroke in patients with significant risk of cardio-embolism, such as higher-risk nonvalvular atrial fibrillation,<sup>74</sup> let alone valvular atrial fibrillation.

The use of anticoagulant therapy in acute ischemic stroke has not been completely abandoned by some. Camerlingo and colleagues<sup>75</sup> reported some benefit with intravenous heparin administered within 3 hours of a nonlacunar stroke, although the increased risk of symptomatic intracerebral hemorrhage tended to negate this benefit. This benefit was also suggested by the TOAST study,<sup>69</sup> which reported some potential benefit from danaparoid in large-artery occlusive disease. Moonis and Fisher<sup>76</sup> have addressed the potential benefit of unfractionated heparin and low-molecular-weight heparin in such circumstances whereby the risk of early recurrent stroke, on an embolic mechanism, is quite substantial. In reference to this, Hallevi and colleagues<sup>77</sup> reported that warfarin could generally be safely started shortly after cardioembolic stroke, whereas heparin and enoxaparin bridging enhances the risk of serious bleeding. Other than for the protection against recurrent cardioembolic stroke, anticoagulant therapy is often initiated sooner rather than later in patients with ischemic strokes who have either cerebrovascular dissection,<sup>78</sup> cerebral sinovenous thrombosis,<sup>79</sup> or a well-documented hypercoagulable state<sup>80</sup> whereby it is thought that the potential benefit outweighs the risk of hemorrhagic complications. However, many of these reports of the potential salutary effect on outcome have been somewhat conflicting, although the benefits of anticoagulation in venous thrombosis are generally supportive both on theoretical grounds as well as clinically.<sup>81</sup>

## ULTRASOUND-ENHANCED THROMBOLYSIS

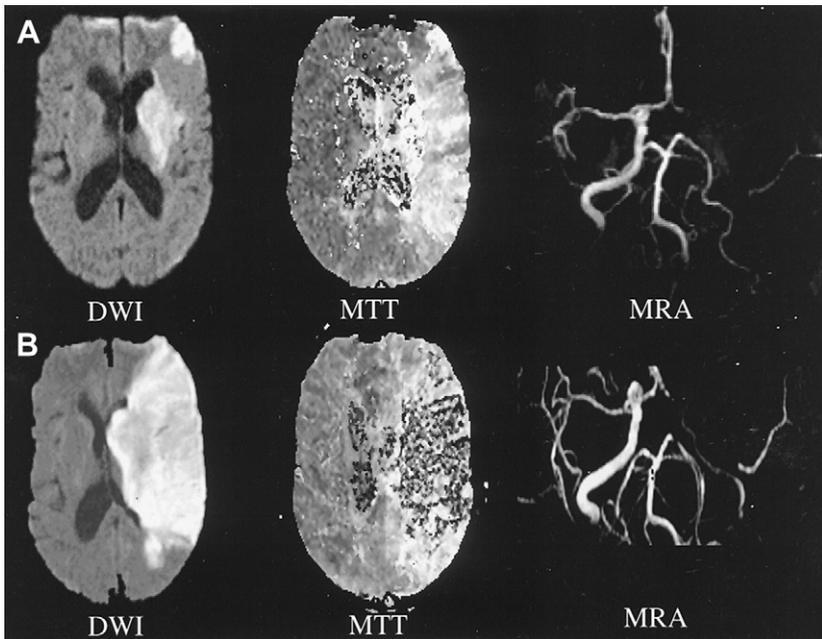
It has been observed experimentally that ultrasound exposure can promote the disruption of fibrin deposition within thrombus formation, which can theoretically promote greater penetration of thrombolytic material into the clot.<sup>4,82</sup> This finding has led to the use of a low MHz-KHz-frequency ultrasound exposure in the clinical setting of acute ischemic stroke treatment, and it has been reported that the administration of microbubbles, in combination with ultrasound, can enhance the clot lysis.<sup>4</sup> Alexandrov and colleagues<sup>83</sup> compared the application of continuous 2-MHz transcranial Doppler ultrasonography with placebo in 126 patients being treated with intravenous rt-PA for acute ischemic stroke. Complete recanalization or dramatic clinical recovery within 2 hours of the administration of the thrombolytic agent was seen in 49% of study patients versus 30% of controls ( $P = .03$ ). However, there has been concern that such therapy can also increase the risk of hemorrhagic transformation of the infarct,<sup>84</sup> and this has been the major limitation in wider applications of this modality. According to one recent study,<sup>85</sup> the combination of 3 doses of 2.5 g of microbubbles with continuous TCD monitoring for 2 hours was reported to enhance reperfusion, but also hemorrhagic transformation of the infarct, but not necessarily the risk of symptomatic intracranial hemorrhage.

## EVALUATION AND TREATMENT OF CEREBRAL EDEMA ASSOCIATED WITH ISCHEMIC STROKE

There are several potential explanations for deteriorating stroke manifestations in patients who present with a mild to moderate deficit.<sup>86</sup> Naturally, clinical worsening associated with recurrent stroke can be seen with a high-risk source of cerebral embolism or an ongoing malicious hypercoagulable state, along with aggressive cerebral vasculitis or propagation of the thrombus that can be seen as part of the pathogenesis of vascular dissection. However, the most common mechanism is probably the evolution of the infarction as part of the ischemic cascade, with development of cytotoxic edema in the area of infarction. The swelling of the infarct tends to peak over 3 to 5 days and can lead to rapid deterioration in death especially in clinical scenarios, such as the malignant middle cerebral artery syndrome.<sup>87</sup>

General measures to address increased intracranial pressure, such as hyperventilation, mannitol,<sup>88</sup> hypertonic (10%) saline,<sup>89</sup> high-dose barbiturates,<sup>90</sup> and steroids, are not necessarily beneficial in such a setting, although they are not infrequently used to buy time against this irreversible process.<sup>90</sup> Hypothermia may have at least a temporary benefit for severe brain swelling associated with massive cerebral infarction (Fig. 5).<sup>91</sup>

Hemicraniectomy is now accepted as a means to improve both mortality and outcome in massive middle cerebral artery infarcts based on the pooled analysis of 3 randomized trials.<sup>92</sup> This compilation, looking at 93 patients aged 60 years or younger, with surgical decompression within 48 hours of stroke onset versus no intervention, found a mortality rate of 22% compared with 71% favoring decompression. Furthermore, moderate to severe disability or death was also in favor of decompression



**Fig. 5.** Evolution from time of presentation (A) and 24 hours later (B) of a massive cerebral hemispheric infarction as demonstrated by diffusion-weighted (MR) imaging and mean transit time (MTT) related to ipsilateral internal carotid artery occlusion by magnetic resonance angiography (MRA).

(57% vs 79%). In addition, suboccipital decompressive craniectomy can be a lifesaving measure with malignant cerebellar infarction.<sup>93</sup> Naturally, one has to keep in perspective the expectations of patients and their families in terms of the potential for the promotion of severe, longstanding functional morbidity with such interventions.

## SUMMARY

The past 40 years have seen the evolution of acute ischemic stroke management from the unproven therapies du jour, such as steroids, heparin for stroke in evolution, and hypervolemic-hemodilution, to more of a scientific basis for our decision-making process.<sup>8</sup> This evolution has been directly related to the advancements in imaging of stroke from the early days of CT brain scan to the presently available MR and CT techniques that allow for both assessment of tissue viability and for circulatory compromise in a matter of minutes. In addition, it has been related to carefully designed, controlled clinical trials of potential therapies, which have led to the recognition of the benefits of thrombolytic therapy in the acute setting but have also left us bemused and frustrated over the lack of benefit for several potential neuroprotective agents that have been studied that seemed to have significant promise at one time.

The art and science of stroke therapy is still in evidence with the newer interventional tools that have become available. We know, by studies and by commonsense, that the effective reestablishment of blood flow with various endovascular techniques should improve outcomes in stroke if the restoration of flow can be achieved while there is ample viable tissue to salvage. It is not out of the realm of possibility that we may soon develop combined approaches that reestablish blood flow and protect the brain from possible adverse consequences of reperfusion, and this remains a very exciting aspect of acute ischemic stroke management. However, it is always important to keep things in perspective in view of the recent NINDS Clinical Alert for angioplasty combined with stenting in the recently halted Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS), which reflected an unacceptably high mortality rate when compared with aggressive medical therapy for symptomatic high-grade intracranial stenosis.

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