Treating Acute Ischemic Stroke

Establishing acute stroke teams and centers and educating family practitioners and emergency room physicians is imperative.

BY GERALD WYSE, MD, AND KIERAN P. MURPHY, MD

Stroke is a leading cause of death and disability in the developed world. More than 750,000 strokes occur in the US annually,[1,2] and one third of these patients die in the first few months after their strokes. For the patient, a stroke is devastating, with problems including loss of mobility, independence, and communication and comprehension skills, leading to a huge cost in health care and lost productivity. Acute stroke treatment is now a reality. Both intravenous (IV)[1] and intra-arterial (IA)[3] thrombolysis have been shown to be effective treatment options that improve patient outcomes.

Unfortunately, because of a narrow therapeutic window, most patients receive no acute stroke treatment. As hospitals change from providing support care to acute treatment, we must increase public awareness that stroke is an acute medical emergency. Time is brain. Establishing acute stroke teams and centers and educating family practitioners and emergency room physicians is imperative for progress to be made in acute stroke treatment and cannot be overstated.

A wide range of endovascular techniques and devices are now at the disposal of the interventionist, giving the interventional radiologist a pivotal role in one of the most common diseases.

CLINICAL PRESENTATION

Patients present with a wide variety of symptoms depending on the vascular territory involved, the amount of clot present, and the presence or absence of collateral vessels. Common symptoms include weakness, numbness, dizziness, blurred vision, and speech and comprehension problems. Stroke is painless, and most patients are unaware of their symptoms, which delays presentation during the critical first few hours. The National Institute of Health Stroke Scale converts the neurologic

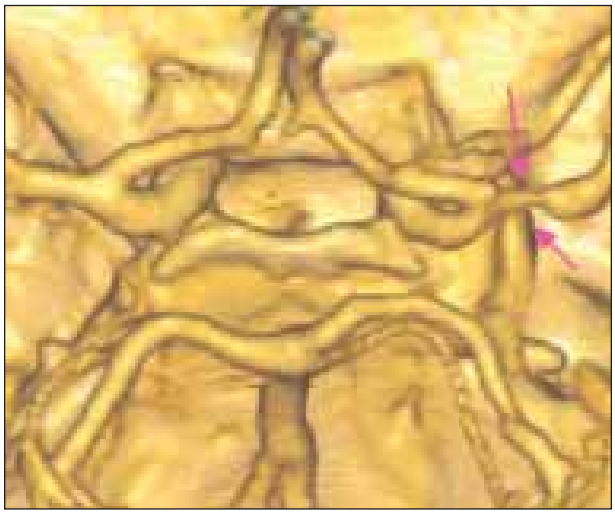

Figure 1. CTA showing vascular pathology in the form of a proximal left MCA stenosis (arrows).

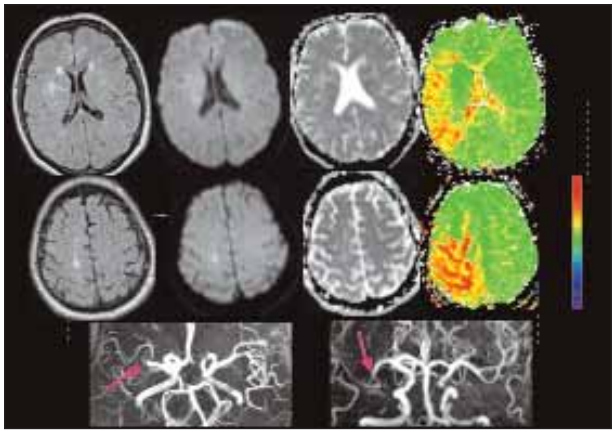

Figure 2. A right middle cerebral artery (MCA) occlusion (arrows) on MRA, ideal for acute treatment with a perfusion/diffusion mismatch.

examination into a reproducible guide to treatment and prognosis. Patients with scores <4 are usually not treated, and patients with scores >20 have a poor prognosis. A multidisciplinary approach is key. Stroke intervention teams streamline diagnosis and therapy to improve patient outcomes.[4]

PATHOPHYSIOLOGY OF ISCHEMIC STROKE

The majority of ischemic strokes are due to cardiogenic embolism and atherosclerotic occlusions of the cranial vessels, which produce a core of infarcted brain tissue that is surrounded by hypoxic but potentially salvageable tissue called the *ischemic penumbra*.[5] The goal of treatment is rapid restoration of blood flow to preserve the ischemic penumbra.

IMAGING

The goal of imaging is to first confirm diagnosis and rule out other conditions that can mimic stroke. In addition, we can now accurately assess brain, metabolism, perfusion, and anatomy to see who will benefit from treatment and in whom thrombolytic treatment should be avoided. If acute treatment is being considered, there is little time to perform such physiologic and anatomic imaging.

CT

CT is readily available, rapid, and ideally suitable for stroke imaging. A stroke protocol generally includes noncontrast CT, CT angiography, and CT perfusion.

Noncontrast CT is performed to diagnose hemorrhagic stroke and to rule out other conditions such as subarachnoid hemorrhage.[6] Physicians should look for the subtle signs of cerebral infarction, including hypoattenuation of the gray matter—in effect, blurring of the gray-white matter junction, sulcal compression, and hyperattenuating arteries. If these findings are present in more than one third of the MCA territory, thrombolysis will likely result in a poor outcome.[1]

CTA should be performed from the aortic arch to the skull vertex. It will detect large-vessel occlusions with high sensitivity and will confirm clot location and surrounding vascular pathology—all of which can help to plan for intervention (Figure 1).

CT perfusion reveals the hemodynamic status of the brain and the quality of the collateral vessels. Time to peak and cerebral blood flow are thought to represent the ischemic area, and cerebral blood volume presents a core infarct and correlates well with the final infarct size. A cerebral blood flow/volume mismatch represents salvageable tissue. This concept may be oversimplified, but in general this method can be applied.

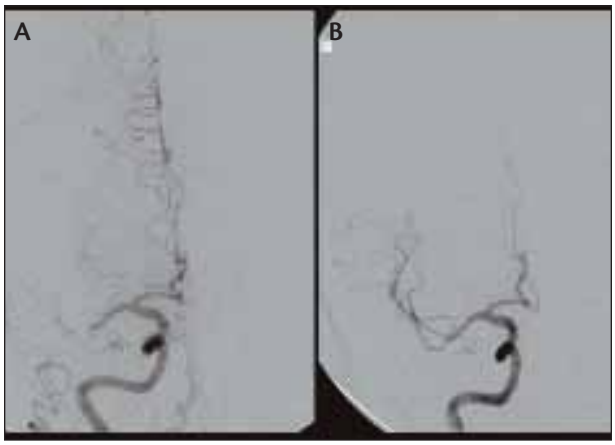

Figure 3. The right MCA before (A) and after (B) the administration of 10 mg of tissue plasminogen activator (tPA) from a microcatheter.

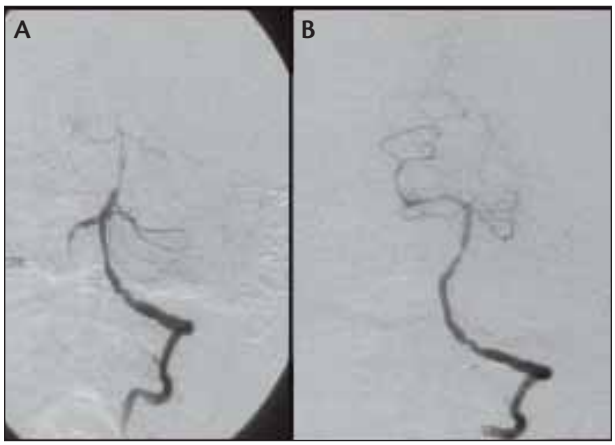

Figure 4. The basilar artery before (A) and after (B) tPA administration from the vertebral artery origin.

MRI

Diffusion-weighted imaging (DWI) is based on the micromolecular motion of water. Ischemic areas appear as hyperintense on DWI and hypointense on apparent diffusion coefficient maps. DWI is more sensitive and specific than CT for detection of ischemia during the first few hours after a stroke;[7] it is a better predictor of the ischemic core. MRI is ideal for assessment of the posterior fossa and brainstem, which is not possible with CT due to bony artifacts.

Problems do arise when using MRI in the setting of acute stroke. These include lack of availability, contraindications, longer scanning time, and motion artifacts in an uncooperative patient.

Most protocols include DWI, perfusion-weighted imaging, Flair, T2, T2*, MR angiography, and postgadolinium imaging. These modalities can be time-consuming and nonproductive in a uncooperative patient. A hyper-

acute protocol with DWI and perfusion-weighted imaging can often be used to decide if urgent IA thrombolysis is appropriate.

In most cases, DWI shows irreversible ischemia; perfusion imaging shows the entire ischemic region. A diffusion-perfusion mismatch represents the ischemic penumbra or salvable tissue (Figure 2).[8]

Catheter Angiography

It is important to fully understand brain perfusion prior to any intervention. Cerebral angiography will better define the degree of occlusion and will reveal the morphology of the thrombus. Determining the presence or absence of patent communicating vessels and collateral pathways is critical before administration of thrombolytic treatment. If the CT or MRI does not view the aorta, it is necessary to perform arch aortography, which will save time and contrast in navigating through difficult vasculature. Carefully examining the parenchymal phase of the cerebral angiogram is an inexpensive but dynamic perfusion study. Crossing occluded carotids is dangerous and unnecessary if adequate collateral vessels in the circle of Willis are present. In this situation, breaking up thrombus can worsen brain perfusion.

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IV THROMBOLYSIS

As a result of the findings of the NIND-IV tPA trial, IV tPA has been licensed since 1996. IV tPA is safe and effective for treating stroke within 3 hours from the onset of symptoms. Patients who receive treatment are 30% more likely to have minimal or no disability.[1] Other trials using IV thrombolytics >3 hours after the onset of symptoms have shown no benefit.[9-11] Unfortunately, because of this narrow time window, only 3% to 5% of patients in the US receive IV treatment.[11] IV thrombolytics have also shown to be less effective when the clot burden is large.[12]

IA THROMBOLYSIS

Intracranial thrombolytic treatment is effective, and improves patient outcomes,[3,13] and it can be administered

in the anterior circulation up to 6 hours after the onset of symptoms. Stroke in the posterior circulation has a dismal outcome. Basilar occlusion has an 80% to 90% mortality rate,[14] and because of this high rate, intervention in the posterior circulation is considered reasonable even up to 24 hours after the onset of symptoms. This larger therapeutic window means more patients are potentially treatable.

The re-establishment of blood flow can be seen using this modality, allowing for drug infusion to be stopped. Higher, local-drug concentrations in the occluded vessel and lower systemic concentrations can be achieved. In addition, a higher rate of recanalization compared to IV thrombolytics has been reported.[15]

Unfortunately, IA thrombolytic treatment is costly, and not every center can provide 24-hour coverage. Compared to IV treatment, the need to assemble the interventional team can cause a delay. Several trials have shown promise in a combined IV and IA approach.[16] However, if this combined approach involves transferring patients, it usually takes longer than planned.

TABLE 1. METHODS OF AUGMENTING THROMBOLYSIS

- **Mechanial thrombus disruption:** Simply passing the microcatheter and microwire several times through the thrombus will expose the thrombolytic drugs to a greater surface area (Figure 3).[17]
- **Ultrasound (MicroLysUS catheter, EKOS Corporation, Bothell, WA):** A cylindrical ultrasound transducer at the tip of the microcatheter augments thrombolytic drugs.[18]
- **Angioplasty and stenting:** Both balloon angioplasty and stenting have been successfully used to restore blood flow in the setting of acute stroke.[19] Stenting a vertebral artery origin or a carotid bifurcation can increase brain perfusion and lead to reversal of ischemia.[14]
- **Thrombectomy:** Suction thrombectomy using a 7-F to 8-F guiding catheter is only suitable for acute carotid occlusion. A variety of snares, such as the 4-mm Gooseneck snare (ev3 Inc., Plymouth, MN), have been used to entangle and remove thrombus from intracranial vessels.[20]
- **AngioJet/NeuroJet (Possis Medical, Inc., Minneapolis, MN):** Combines local vortex suction with mechanical disruption. These devices have been successfully used to treat acute carotid occlusions.[21]
- **Merci Retriever (Concentric Medical, Inc., Mountain View, CA):** This platinum-tipped nitinol wire forms a gradually enlarging helix and is deployed via a microcatheter. A 9-F balloon-tipped guiding catheter is used for flow arrest; two or three loops of wire are deployed distal to the thrombus. It is then pulled back to engage the thrombus, and the remaining loops are deployed to capture the thrombus.[22,23]

ENDOVASCULAR OPTIONS

There are many ways to augment thrombolysis (Table 1). Multiple techniques and devices are available to the interventional radiologist. Mechanical thrombolysis may be used to remove the occluding thrombus and rapidly restore blood flow. This may lead to a reduction or elimination of the use of potentially harmful thrombolytic drugs. However, intracranial navigation of these devices can be difficult, and there is an increased risk of vessel wall damage, perforation, and device fracture.

POSTPROCEDURE

The immediate postprocedure management is as crucial as the treatment itself. Patients should be transferred to an intensive care unit or a specialized stroke unit capable of performing rapid and frequent neurological assessment.[24] Urgent CT should be readily available. The management of intracranial pressure, blood pressure, temperature, and blood glucose is critical. Anticoagulation or aspirin have not been shown to improve outcomes.[25]

TREATING STROKE IN COMMUNITY HOSPITALS

It is unrealistic and unlikely that all acute hospitals can provide 24-hour interventional radiology services. There are simply not adequately trained staff or equipment available, which leads to the concept of appropriate levels of intervention for these types of hospitals. The interventional radiologist can administer tPA from the proximal internal carotid artery for MCA occlusion or the vertebral artery origin for basilar thrombosis with reasonable success (Figure 4).

CONCLUSION

Although the ideal thrombolytic agent, dose, and timing are still unknown, acute stroke treatment using thrombolytic agents—both IV and IA—is effective and safe in selected patients. A narrow therapeutic window requires streamlined diagnosis and treatment. A variety of endovascular techniques and devices are now available to augment thrombolysis in the brain. Hospitals need to provide acute stroke treatment at a level that is appropriate for their staff and equipment. By providing a stroke service, the interventional radiologist is a fundamental element in improving patient outcomes after a potentially devastating event. ■

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1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581-1587.
2. Higashida RT, Connors JJ III. Should interventional radiologists be involved in acute stroke intervention? J Vasc Interv Radiol. 2001;12:145-146.
3. Furlan A, Higashida, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA. 1999;282: 2003-2011.
4. Fagan SC, Morgenstern LB, Petitta A, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. Neurology. 1998;50:883-890.
5. Heiss WD, Thiel A, Grond M, et al. Which targets are relevant for therapy of acute ischemic stroke? Stroke. 1999;30:1486-1489.
6. Culebras A, Kase CS, Masdeu JC, et al. Practice guidelines for the use of imaging in transient ischemic attacks and acute stroke. A report of the Stroke Council, American Heart Association. Stroke. 1997;28:1480-1497.
7. Provenzale JM, Sorensen AG. Diffusion-weighted MR imaging in acute stroke: theoretic considerations and clinical applications. Am J Roentgenol. 1999;173:1459-1467.
8. Provenzale JM, Jahan R, Naidich TP, et al. Assessment of the patient with hyperacute stroke: imaging and therapy. Radiology. 2003;229:347-359.
9. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017-1025.
10. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet. 1998;352:1245-1251.
11. Clark WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA. 1999;282:2019-2026.
12. del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol. 1992;32:78-86.
13. Zeumer H, Hacke W, Ringelstein EB. Local intraarterial thrombolysis in vertebrobasilar thromboembolic disease. Am J Neuroradiol. 1983;4:401-404.
14. Lin DD, Gailloud P, Beauchamp NJ, et al. Combined stent placement and thrombolysis in acute vertebrobasilar ischemic stroke. Am J Neuroradiol. 2003;24:1827-1833.
15. Mori E, Yoneda Y, Tabuchi M, et al. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. Neurology. 1992;42:976-982.
16. Lewandowski CA, Frankel M, Tomsick TA, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. Stroke. 1999;30:2598-2605.
17. Barnwell SL, Clark WM, Nguyen TT, et al. Safety and efficacy of delayed intraarterial urokinase therapy with mechanical clot disruption for thromboembolic stroke. Am J Neuroradiol. 1994;15:1817-1822.
18. Mahon BR, Nesbit GM, Barnwell SL, et al. North American clinical experience with the EKOS MicroLysUS infusion catheter for the treatment of embolic stroke. Am J Neuroradiol. 2003;24:534-538.
19. Nedeltchev KC, Brekenfeld C, Remonda L, et al. Internal carotid artery stent implantation in 25 patients with acute stroke: preliminary results. Radiology. 2005;237:1029-1037.
20. Nesbit GM, Luh G, Tien R, et al. New and future endovascular treatment strategies for acute ischemic stroke. J Vasc Interv Radiol. 2004;15(1 Pt 2):S103-110.
21. Bellon RJ, Putman CM, Budzik RF, et al. Rheolytic thrombectomy of the occluded internal carotid artery in the setting of acute ischemic stroke. Am J Neuroradiol. 2001;22:526-530.
22. Martinez H, Zoarski GH, Obuchowski AM, et al. Mechanical thrombectomy of the internal carotid artery and middle cerebral arteries for acute stroke by using the retriever device. Am J Neuroradiol. 2004;25:1812-1815.
23. Flint AC, Duckwiler GR, Budzik RF, et al. Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials. Stroke. 2007;38:1274-1280.
24. Langhorne P, Williams BO, Gilchrist W, et al. Do stroke units save lives? Lancet. 1993;342:395-398.
25. Brott T, Bogousslavsky J. Treatment of acute ischemic stroke. N Engl J Med. 2000;343:710-722.