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Authors:

Bentley J. Bobrow, MD, FACEP, Clinical Associate Professor, Emergency Medicine Department, Maricopa Medical Center, Phoenix, AZ; Medical Director, Bureau of EMS and Trauma System, Arizona Department of Health Services, Phoenix.

Shadi Rafael, Medical Student, University of Arizona College of Medicine, Tucson.

Peer Reviewer:

Joseph Shiber, MD, FACP, FACEP, Associate Professor, University of Florida, Jacksonville.

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AHC Media

Emergency Department Evaluation of Stroke and TIA: Beyond the CT Scan: Part II

This issue of Emergency Medicine Reports *is the second in a two-part series on imaging and evaluation of stroke and transient ischemic attack (TIA). Part 1 reviewed risk factors, history and physical examination, and computed tomography (CT) imaging. This part will review magnetic resonance imaging (MRI) and ultrasound techniques, and treatment.*

—J. Stephan Stapczynski, MD, FACEP, Editor

Magnetic Resonance Imaging

MRI technology has advanced considerably since its emergence in the 1970s, with the development of higher resolution images and the development of various pulsing sequences that allow for a more detailed examination of brain tissue. The typical MRI examination today includes a combination of sequences such as T1, T2, spin-density, gradient echo (GRE), fluid attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and perfusion-weighted imaging (PWI), performed in 15 to 20 minutes with conventional machines or 5 minutes or less by newer, ultrafast MRI technology. One major advantage of using MRI as compared to CT for the evaluation of stroke is the use of a magnetic field instead of ionizing radiation, which spares patients from the potential harmful effects of radiation exposure. Its limitations include patient contraindications (e.g., pacemakers, metal implants) and intolerance (claustrophobia), higher cost, lack of uniform availability, longer acquisition time, need for MRI-compatible monitoring equipment, and staffing requirements for a 24-hour MRI unit.

MRI can accomplish the same goals as CT, namely to exclude the presence of hemorrhage in or around the brain, detect ischemic cerebral tissue, and exclude stroke mimics. The ability of MRI to accomplish these functions differs within the various pulsing sequences. Conventional MRI sequences (T1, T2, and spin-density) alone are at least as sensitive when compared to CT in detecting ischemia and acute intracerebral hemorrhage (ICH).[1,2] (*See Table 1.*) The addition of other pulsing sequences enhances the sensitivity for early ischemia and chronic hemorrhage. For the detection of subarachnoid hemorrhage (SAH), however, CT is still the preferred modality. Even though FLAIR has been shown to detect SAH, no prospective, randomized studies have been performed to compare its efficacy to the traditional non-contrast CT (NCCT).[3,4] Finally, for detecting stroke mimics such as neoplasms, infections, cerebral edema, and inflammatory diseases, MRI has a higher sensitivity and specificity.[5]

Gradient Echo MRI (GRE-MRI). GRE, a type of MRI sequence, utilizes susceptibility differences in tissues and generates images with phase contrast. The primary use of GRE is the detection of ICH; GRE has been shown to be at least equivalent to CT for detecting acute hemorrhage. In detecting chronic hemorrhage and microbleeds, however, it is superior to NCCT.[6]

Executive Summary

- MRI with diffusion-weighted imaging is recommended for the imaging of ischemic stroke presenting within 3 hours of symptom onset.
- CTA is the best imaging modality to identify both extracranial and intracranial arterial obstructive lesions.
- Risk-stratification tools can be used to identify TIA patients appropriate for outpatient evaluation.
- Intra-arterial fibrinolytics or endovascular interventions may be helpful in selected ischemic stroke patients ineligible for intravenous rtPA.

Additionally, GRE may be more sensitive than CT in detecting hemorrhagic transformation of ischemic stroke.[6] GRE is utilized mainly in academic tertiary centers, while most community hospitals continue to use NCCT for detection of ICH. However, as more centers begin to use MRI techniques for earlier and faster detection of ischemia, the need to obtain an NCCT for the detection of ICH may be decreased with the use of GRE-MRI.

Diffusion-Weighted Imaging (DWI-MRI). DWI is obtained by detecting water movement. The radiofrequency pulses of water molecules between two close locations are measured in various areas of the brain and translated into a diffusion map. The advantage of this image sequence is that it can detect cerebral ischemia earlier than CT or conventional MRI. As early as 3 to 30 minutes after the onset of ischemia, diffusion becomes restricted in cerebral tissue and visible on DWI.[7-9] DWI-MRI has a sensitivity of 91% and a specificity of 95% to detect ischemia within 6 hours of symptom onset — rates that are superior to those seen with FLAIR, T2 MRI, or CT.[10-14] Figure 1 shows an example of cerebral infarction as detected on DWI.

The American Academy of Neurology (AAN) published new imaging guidelines in 2010 recommending the use of DWI for the diagnosis of acute ischemic stroke in patients presenting within 12 hours of symptom onset. The American Stroke Association (ASA) similarly recommends the use of either DWI or CT angiography source images (CTA-SI) for the diagnosis of ischemic stroke in patients presenting within 3 hours of symptom onset if the acquisition of these images does not "unduly delay the administration of intravenous tPA."[3] DWI is also the preferred imaging modality in evaluation of TIA patients because it allows for improved accuracy of diagnosis.[15]

Table 1: Brain Imaging with Conventional MRI Sequences

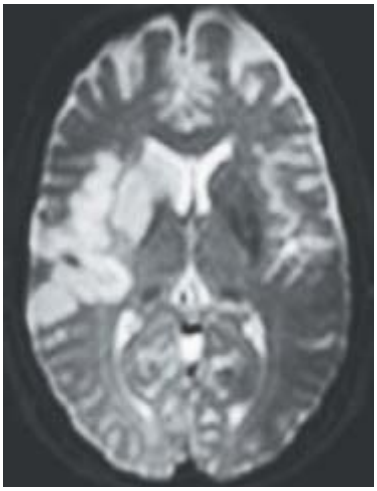
	Water and CSF	Brain	Blood (acute < 6 h)	Ischemia (compared to nonischemic areas)
T1 images	Black	White matter brighter than gray matter	Gray	Darker gray
T2 images	White	Gray matter brighter than white matter	Light gray	Lighter gray
Spin-density (proton density) images	Dark gray	Gray matter brighter than white matter	Dark gray	Darker gray

Despite these new recommendations, many facilities continue to use CT studies for the evaluation of acute ischemic stroke in the ED.[16] In addition to the previously mentioned disadvantages of MRI, many centers have resisted the implementation of MRI for stroke diagnosis because they have already-established stroke protocols utilizing CT studies. Although obtaining an MRI is more expensive than a CT scan, changes in clinical processes that allow immediate access to the MRI scanner will eventually obviate the need to obtain a "preliminary" CT scan and will yield a more accurate diagnosis, and may ultimately prove to be cost effective. Some also argue that the time required to perform the various MRI pulsing sequences far exceeds that needed to acquire CT images. A study by Schellinger et al,[17] however, showed that an exam consisting of DWI, FLAIR, GRE, PWI, and MRA can be performed in 15 to 20 minutes, which is comparable to the 15 minutes of time required to obtain the CT equivalent with NCCT, CTA/CTA-SI, and CTP.[18]

Perfusion-Weighted Imaging (PWI). PWI, also called magnetic resonance perfusion (MRP), creates a perfusion map of the brain through the use of intravenous gadolinium contrast that traverses the cerebral vasculature. Images are obtained every 1 to 2 seconds over the time it requires the contrast to move through the vasculature.

The most valuable application of PWI is perhaps in construction of diffusion/perfusion maps using data from DWI and PWI studies. Areas of mismatch (hypoperfusion volume on PWI greater than ischemic volume on DWI) may represent the physiological penumbra where salvageable tissue is present. These

Figure 1: Diffusion-Weighted Imaging



Diffusion-weighted imaging obtained 2 days after the onset of ischemic stroke in the territory of the right middle cerebral artery demonstrates a hyperintense lesion in the temporal and frontal lobes and in the basal ganglia. Similar changes may be observed in the first hours after the onset of symptoms.
Reprinted with permission from: van der Worp HB, van Gijn J. Acute ischemic stroke. *N Engl J Med* 2007;357:572-579.

data can then be used in selecting patients who may benefit most from intravenous or intra-arterial thrombolysis. Additionally, diffusion/perfusion maps have been shown to have utility in determining patient outcome.[19]

Although PWI and its derived parameters (including diffusion/perfusion mapping) are used in practice, the diagnostic and clinical utility of these perfusion techniques has not yet been demonstrated in high-level studies.[3,20] In its recently published guidelines, the AAN stated that there is "insufficient evidence to support or refute the value of PWI in diagnosing acute ischemic stroke."[21] Despite its current ambiguous utility, perfusion imaging has shown great potential in precisely defining the extent of tissue injury in acute cerebral ischemic events and has been at the forefront of the new wave of stroke imaging techniques. Ongoing research in this area aims to validate perfusion techniques for use in the clinical setting.

Magnetic Resonance Angiography (MRA). Magnetic resonance angiography is used similarly to CTA to detect vascular stenosis or occlusion of intracranial and extracranial vessels. Additionally, MRA has some function in detecting arterial dissection, fibromuscular dysplasia, vasculitis, arteriovenous malformations, and intracranial aneurysms. Gadolinium-enhanced MRA is rapidly replacing nonenhanced MRA techniques due to its superior sensitivity (86% to 99% vs. 93%) in detecting extracranial stenosis.[3] Whether the same holds true for the use of contrast-enhanced MRA in detecting intracranial stenosis is currently under study. Nonenhanced MRA has a sensitivity of 60% to 90% for detection of intracranial stenosis and occlusion.[22]

When compared to CTA, MRA is equivalent for detecting extracranial lesions, and both surpass the ability of Doppler ultrasound. In detecting intracranial lesions, however, CTA has a higher sensitivity and positive predictive value than MRA.[22]

Ultrasound Methods

Ultrasound methods such as carotid duplex ultrasound (CDUS) and transcranial Doppler (TCD) are widely available, noninvasive methods of evaluating extracranial and intracranial large vessels, respectively, for the presence of stenosis or occlusion. Historically, these methods have been used for the evaluation of subacute stroke and secondary stroke prevention. Nonetheless, studies show that they can function in a similar capacity in the acute phase of stroke evaluation and aid in the selection of patients for interventional thrombolysis.[23-25] Their use, however, is limited by a number of factors, including suboptimal detection capabilities as compared to CTA and MRA, longer acquisition time than NCCT, operator dependence, and availability of experienced ultrasonographers in the acute setting.

Summary of Imaging Recommendations

It is important that practicing EPs be aware of current and evolving cerebrovascular imaging techniques, strategies, and guidelines for the evaluation of acute stroke and TIA in order to ensure the best outcome for patients. If advanced imaging techniques are available, their acquisition should not delay the administration of tPA in eligible patients. The guideline goal is that imaging for acute stroke be obtained within 25 minutes of the patient's arrival to the ED and interpreted within 45 minutes from time of arrival. Table 2 provides a comparison of the various imaging techniques previously discussed and can help EPs tailor diagnostic imaging to specific patients within the available resources of their clinical site.

For the evaluation of hemorrhagic stroke, imaging preferences depend on the suspicion for SAH vs. ICH. For the detection of SAH, NCCT is recommended. However, if MRI is being used to image the patient, the FLAIR sequence may be an adequate substitution. For the detection of acute ICH, NCCT is nearly equivalent to MRI. The GRE sequence of MRI, however, detects chronic hemorrhage and hemorrhagic transformation better than CT.

For the evaluation of ischemic stroke, DWI is superior to other imaging modalities in the early phase (within 12 hours of symptom onset). CTA-SI, however, comes close to DWI in sensitivity for detecting acute ischemia, especially in medium to large infarcts. NCCT, on the other hand, can miss as many as one-third of early cases of ischemia (within 3 hours of onset).

In imaging the cerebral vasculature, CTA and MRA are more sensitive than ultrasound techniques. The two noninvasive angiography techniques are nearly equivalent, except for imaging the intracranial vessels, where CTA has a higher accuracy rate than MRA. Conventional

Table 2: Comparison of Neuroimaging Techniques for Acute Stroke and TIA

Imaging Technique	Recommended Use	Main Characteristics	Notes
CT Imaging Techniques			
Non-contrast Computed Tomography (NCCT)	• Detection of hemorrhage • Detection of ischemia • Detection of intracranial malignancy or abscess	• Sensitivity (acute hemorrhage): +++ • Sensitivity (acute ischemia): + • Sensitivity (intracranial mass/abscess): ++ • Radiation exposure: Yes • IV contrast: No • Time to acquisition of images: ⌛ • Availability: +++ • Cost: $	• Reliable EP interpretations • Low detection rate of ischemia in the posterior circulation • Misses 1/3 of early ischemia (within 3 hours of onset)
CT Angiography (CTA)	Detection of intra- and extra-cranial vascular pathology	• Sensitivity (vascular pathology): +++ • Radiation exposure: Yes • IV contrast: Yes • Time to acquisition of images: ⌛ • Availability: +++ • Cost: $	
CTA Source Images (CTA-SI)	• Detection of intra- and extracranial vascular pathology • Detection of ischemia • Detection of cerebral perfusion abnormalities	• Sensitivity (vascular pathology): +++ • Sensitivity (acute ischemia): ++ • Sensitivity (perfusion abnormalities): +++ • Radiation exposure: Yes • IV contrast: Yes • Time to acquisition of images: ⌛ • Availability: +++ • Cost: $	• Obtained concurrently with CTA • Superior to NCCT in detection of early ischemia, and nearly as sensitive as DWI • May miss small foci of ischemia, especially in the posterior circulation
CT Perfusion (CTP)	Detection of cerebral perfusion abnormalities	• Sensitivity (perfusion abnormalities): ++ • Radiation exposure: Yes • IV contrast: Yes • Time to acquisition of images: ⌛ • Availability: ++ • Cost: $	Application of perfusion techniques to treatment and outcome is unclear
Multimodal CT (NCCT + CTA + CTP)	• Detection of hemorrhage • Detection of ischemia • Detection of intracranial malignancy or abscess • Detection of intra- and extracranial vascular pathology • Detection of cerebral perfusion abnormalities	• Sensitivity (acute hemorrhage): +++ • Sensitivity (acute ischemia): ++ • Sensitivity (intracranial mass/abscess): ++ • Sensitivity (vascular pathology): +++ • Sensitivity (perfusion abnormalities): +++ • Radiation exposure: Yes • IV contrast: Yes • Time to acquisition of images: ⌛⌛ • Availability: ++ • Cost: $	• Greater radiation exposure due to longer imaging time • May miss small foci of ischemia, especially in the posterior circulation

(*Continued*)

Table 2: Comparison of Neuroimaging Techniques for Acute Stroke and TIA (continued)

Imaging Technique	Recommended Use	Main Characteristics	Notes
MR Imaging Techniques			
Magnetic Resonance Imaging (MRI)	• Detection of hemorrhage • Detection of ischemia • Detection of intracranial malignancy or abscess	• Sensitivity (acute hemorrhage): +++ • Sensitivity (acute ischemia): + • Sensitivity (intracranial mass/abscess): +++ • Radiation exposure: No • IV contrast: No • Time to acquisition of images: ⌛⌛ • Availability: ++ • Cost: $$$	Patient contraindications (e.g., pacemakers, metallic implants) and intolerance (claustrophobia) may interfere with image acquisition
Gradient Echo (GRE-MRI)	Detection of hemorrhage	• Sensitivity (acute hemorrhage): +++ • Radiation exposure: No • IV contrast: No • Time to acquisition of images: ⌛⌛⌛ • Availability: + • Cost: $$$	• Beware of patient contraindications and intolerance • More sensitive than NCCT in detection of hemorrhagic transformations, chronic hemorrhage, and microbleeds
Diffusion-Weighted Imaging (DWI-MRI)	Detection of ischemia	• Sensitivity (acute ischemia): +++ • Radiation exposure: No • IV contrast: No • Time to acquisition of images: ⌛⌛⌛ • Availability: + • Cost: $$$	• Beware of patient contraindications and intolerance • The most sensitive technique for the detection of early ischemia • Data can be used to construct diffusion/perfusion maps
Perfusion-Weighted Imaging (PWI-MRI)	Detection of cerebral perfusion abnormalities	• Sensitivity (perfusion abnormalities): +++ • Radiation exposure: No • IV contrast: Yes • Time to acquisition of images: ⌛⌛⌛ • Availability: + • Cost: $$$	• Beware of patient contraindications and intolerance • Data can be used to construct diffusion/perfusion maps • Application of perfusion techniques to treatment and outcome is unclear
MR Angiography (MRA)	Detection of intra- and extracranial vascular pathology	• Sensitivity (vascular pathology): +++ • Radiation exposure: No • IV contrast: Optional • Time to acquisition of images: ⌛⌛⌛ • Availability: + • Cost: $$$	• Beware of patient contraindications and intolerance • Use of IV contrast is optional • Slightly lower sensitivity than CTA in detecting intracranial lesions

(*Continued*)

Table 2: Comparison of Neuroimaging Techniques for Acute Stroke and TIA (continued)

Imaging Technique	Recommended Use	Main Characteristics	Notes
Ultrasound Techniques			
Carotid Duplex Ultrasound & Transcranial Doppler	Detection of intra- and extra-cranial vascular pathology	• Sensitivity (vascular pathology): + • Radiation exposure: No • IV contrast: No • Time to acquisition of images: ⧖⧖⧖ • Availability: ++ • Cost: $	• Operator dependence • Requires availability of experienced ultrasonographers in the acute setting

catheter angiography remains the gold standard for evaluation of cerebral vasculature, but it is rarely performed due to its invasive nature and risk of complications.

Perfusion techniques are rapidly evolving and allow for quantification of such parameters as core of initial infarction, volume of salvageable tissue, and diffusion/perfusion mismatch. The accuracy and usefulness of perfusion techniques, however, have not been proven in large, controlled studies.

Imaging goals in the evaluation of stroke and TIA can be best accomplished by MRI and its various pulsing sequences, which are either equivalent or superior in sensitivity compared to CT techniques. There are a number of barriers, however, to the use of MRI technology in the ED for the evaluation of acute stroke and TIA. If such barriers as timing, rapid access to an MRI machine, and patient monitoring can be overcome, the CT scanner can be completely bypassed in the acute evaluation of a stroke or TIA patient and substituted with MRI technology. Widespread availability and implementation of MRI techniques have the potential to improve stroke and TIA patient outcomes via earlier and more sensitive detection of pathologic cerebrovascular processes.

Management and Treatment

Management of patients with suspected TIA or stroke is multifaceted, and treatment modalities are continuously evolving. In recent years, advances such as the extension of the therapeutic window for the administration of intravenous or intra-arterial tPA and recanalization approaches have improved patient outcomes. While a number of acute interventions have shown potential as tools to effectively manage stroke patients, further research and empiric evidence are needed to support implementation of such interventions.

Table 3: Recommended Guidelines for Treating Elevated BP in Spontaneous ICH[26]

Blood Pressure Management in ICH Patients

- **If SBP is > 200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 min.**
- **If SBP is > 180 mm Hg or MAP is > 130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure ≥ 60 mm Hg.**
- **If SBP is > 180 mm Hg or MAP is > 130 mm Hg and there is no evidence of elevated ICP, then consider a modest reduction of BP (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically re-examine the patient every 15 min.**

Intracerebral Hemorrhage. The management of ICH is primarily medical, which, if started early and done aggressively, can have a positive impact on patient outcome.[26] Although surgical interventions for the removal of the hematoma, in theory, would limit injury, there is significant risk associated with the procedure. For most ICH patients, the value of surgery is uncertain. Surgical interventions will not be discussed here, as they are outside of the scope of ED management.

In 2010, the ASA released new guidelines for the management of spontaneous ICH.[26] The recommendations for ED management are outlined below:

- Underlying hemostatic abnormalities (e.g., coagulation factor deficiency, thrombocytopenia, induced anticoagulation) should be rapidly treated with coagulation factors, platelets, and fresh frozen plasma (FFP) plus vitamin K, respectively.
- The treatment of elevated BP in the setting of ICH is a topic of ongoing research. Current recommendations are listed in Table 3.
- Normoglycemia should be maintained.
- Seizures should be controlled with antiepileptic medication. Seizure prophylaxis is not required.
- Subsequent monitoring and management should take place in the intensive care unit (ICU).

Transient Ischemic Attack. The

management of TIA primarily consists of uncovering the underlying cause of the ischemic episode and reducing the risk of a future TIA or stroke through medical or surgical management and reduction of modifiable risk factors. Patients suspected of having suffered an acute TIA should ideally undergo neuroimaging within 24 hours of symptom onset and be evaluated for an etiology no later than 48 hours after the event.[15]

The main concern for the ED physician, after medical stabilization and imaging, is whether outpatient management should be attempted for the patient or if hospital admission is necessary. Considering that there is high early risk of stroke after a TIA, risk stratification plays an important role in deciding whether to admit the patient to the hospital for evaluation. While hospital admission has been shown to be cost-effective for high-risk patients, its benefits are debatable for low- to medium-risk patients.[27] Clinical prediction rules, as a result, play an important role in triaging patients after TIA.[28-30]

The ABCD² score (*Table 4*) is a clinical assessment tool used to predict the risk of stroke within 48 hours of a TIA. The combined score predicts two-day stroke risk as follows:

- Score of 6 to 7: High two-day stroke risk (8%);
- Score of 4 to 5: Moderate two-day stroke risk (4%);
- Score of 0 to 3: Low two-day stroke risk (1%).

This score was derived using two earlier prognostic scores, the California score[31] and the ABCD score,[32] and validated using independent study populations.[29] While the new score can identify a moderate- or high-risk TIA patient with higher accuracy than earlier scores, it suffers from low specificity and suboptimal ability to predict stroke.[29,30] Despite its shortcomings, however, the ABCD² score currently appears to be the best available clinical tool for stratifying stroke risk in TIA patients in the ED. Integration of clinical information can also further enhance the accuracy of stroke risk prediction, as Ay et al showed by using findings from DWI along with the ABCD² score.[33]

Table 4: Calculating the ABCD² Score

Age	
≥ 60 years	1 point
< 60 years	0 points
Blood Pressure	
Systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg	1 point
Systolic < 140 mmHg and diastolic < 90 mmHg	0 points
Clinical Features	
Unilateral weakness	2 points
Isolated speech disturbance	1 point
Other	0 points
Duration of TIA Symptoms	
≥ 60 minutes	2 points
10 to 59 minutes	1 point
< 10 minutes	0 points
Diabetes	
Present	1 point
Absent	0 points

Hospitalization is recommended for TIA patients if they present within 72 hours of the episode and meet any of the following criteria:[15]

- ABCD² score of ≥ 3;
- ABCD² score of 0 to 2 and concern that outpatient follow-up will not be accomplished within 2 days;
- ABCD² score of 0 to 2 along with other evidence indicating focal ischemia as the cause of the episode.

Consequently, the final decision regarding hospital admission must also take into consideration factors such as available resources, patient compliance, and social situation.

Ischemic Stroke. While intravenous tPA is currently the only medical therapy approved by the Food and Drug Administration (FDA) for ischemic stroke, other thrombolytic agents are under investigation, along with various other endovascular interventions and strategies. Current guidelines and recommendations for the management and treatment of ischemic stroke are outlined below.

General Supportive Care. After initial medical stabilization, the patient's oxygen saturation, temperature, blood pressure, blood glucose, and cardiac activity should be monitored.

- Temperature elevations should be treated with antipyretics.
- Management of arterial hypertension (HTN) is controversial. Current guidelines[34,35] indicate:

– Cautious approach to the acute treatment of HTN.

– Initiation of medical treatment of HTN at systolic BP of greater than 220 or diastolic BP of greater than 120, with the goal of reduction of BP by about 20% in the first 24 hours.

– Acute reduction of BP in patients who have other medical indications for the treatment of HTN.

– Maintenance of BP at or below 185/110 in patients otherwise eligible for tPA or other acute invasive interventions.

- The cause of arterial hypotension should be investigated and fluid replacement initiated.
- Alterations in blood glucose should be appropriately treated to achieve normoglycemia.
- Emergency cardiac interventions should be undertaken if indicated by cardiac monitoring.

Intravenous Thrombolysis. In 1996, the FDA approved the use of intravenous recombinant tPA (rtPA) for the treatment of ischemic stroke based on a study carried out by National Institute of Neurological Disorders and Stroke (NINDS) that showed favorable outcome for treated patients.[36] A total of 624 ischemic stroke patients were enrolled in a two-part study based on predetermined criteria (similar to the inclusion/exclusion criteria used today) and were subjected to either rtPA treatment or placebo. While the outcome measures at 24 hours (assessed as neurological recovery or improvement by 4 points on the National Institutes of Health Stroke Scale [NIHSS]) were similar for the tPA and placebo group, the treatment group showed significant improvement (as measured by the Barthel index, modified Rankin scale, Glasgow outcome scale, and the NIHSS) at 3 months compared to the placebo group. Patients treated with rtPA were 30% more likely to have minimal or no disability at 3 months compared to the placebo group. The major complication from treatment was symptomatic brain hemorrhage, which occurred in 6.4% of patients treated with rtPA compared to 0.6% of patients given placebo. In this study, patients were administered rtPA within 3 hours of symptom onset, and the drug was subsequently approved for use within this limited time window.

Since the approval of tPA, the extension of the therapeutic window has been investigated through further studies, with the most recent being a series of three European studies: European Cooperative Acute Stroke Study (ECASS) 1, 2, and 3.[37-39] In 2008, the results of ECASS-3, a multicenter, prospective, randomized, placebo-controlled trial, showed a modest but significant improvement in outcome (defined as a score of 0 or 1 on the modified Rankin scale) for patients treated with rtPA in the 3 to 4.5 hour window after symptom onset (52.4% vs. 45.2% in placebo group).[39] Moreover, these patients did not suffer from a statistically

Table 5: Inclusion and Exclusion Criteria for Administration of tPA[33]

Inclusion Criteria	Exclusion Criteria
• Diagnosis of ischemic stroke causing measurable neurological deficit • Onset of symptoms within 4.5 hours • Age ≥ 18	**Absolute** • Head trauma or prior stroke in previous 3 months • Symptoms suggesting subarachnoid hemorrhage • Arterial puncture at noncompressible site in previous 7 days • History of previous intracranial hemorrhage • Elevated blood pressure (systolic > 185 mm Hg or diastolic > 110 mm Hg) • Evidence of active bleeding on examination • Acute bleeding diathesis, including but not limited to: –Platelet count < 100 000/mm^3 –Heparin received within 48 hours, resulting in aPTT > upper limit of normal –Current use of anticoagulant with INR > 1.7 or PT > 15 seconds • Blood glucose concentration < 50 mg/dL (2.7 mmol/L) • CT demonstrates multilobar infarction (hypodensity > 1/3 cerebral hemisphere) **Relative** • Recent experience suggests that under some circumstances — with careful consideration and weighing of risk to benefit — patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of rtPA administration carefully if any of these relative contraindications is present: • Only minor or rapidly improving stroke symptoms (clearing spontaneously) • Seizure at onset with postictal residual neurologic impairments • Major surgery or serious trauma within previous 14 days • Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days) • Recent acute myocardial infarction (within previous 3 months) **Additional Exclusion Criteria for Patients in the 3 to 4.5 Hour Window:** • Patients older than 80 years • Those taking oral anticoagulants • Those with a baseline NIHSS score > 25 • Those with both a history of stroke and diabetes

rtPA = recombinant tissue plasminogen activator; aPTT = activated partial thromboplastin time; INR = international normalized ratio; and PT = partial thromboplastin time

significant increased risk of intracranial hemorrhage compared to patients in previous studies who were treated with tPA during the initial 3-hour window (7.9% risk in this study vs. average risk of 6% in previous studies[35] for administration of tPA within 3 hours). Following the publication of ECASS-3, the ASA changed its guidelines for the treatment of ischemic stroke to reflect the extension of the tPA therapeutic window to 4.5 hours for eligible patients.[34,40] The use of tPA during the 3 to 4.5 hour window, however, has not yet been approved by the FDA.

Administration of tPA (0.9 mg/kg, maximum dose 90 mg) should be considered for patients satisfying the required criteria (*see Table 5*), and patients should be closely monitored during the treatment phase in the ICU or stroke unit for potential complications such as bleeding and angioedema. Notably, the risk of intracranial hemorrhage increases proportionally with greater deviation from the protocol in Table 5.[41,42] Patients in the 3 to 4.5 hour window are subject to additional exclusion criteria,[40] as outlined in Table 5.

The administration of other thrombolytic agents, outside the setting of clinical trials, is not currently recommended.[35]

Intra-arterial Thrombolysis. Intra-arterial thrombolysis allows for the delivery of a high concentration of a thrombolytic agent into an arterial thrombus. The original study supporting the utility of intra-arterial thrombolysis was performed using recombinant prourokinase for the treatment of patients within 6 hours of a stroke that occurred secondary to an occlusion of the middle cerebral artery (MCA).[43] The use of intra-arterial thrombolysis in these patients led to an arterial recanalization rate of 66% vs. 18% in the control group, with the major complication of treatment being intracranial hemorrhage (reported in 10% vs. 2% in the control group).[43]

Since the original study, potential benefit of intra-arterial thrombolysis has also been suggested for stroke patients with basilar or vertebral occlusion,[44] as well as patients within 6 hours of stroke who have a contraindication for the use of intravenous rtPA.[4,45-47] Recombinant prourokinase, however, has not been approved by the FDA and is not currently available for clinical use. General consensus and case series data have converged on the substitution of rtPA or urokinase in intra-arterial thrombolysis.[35]

Current indications for use of intra-arterial thrombolysis are:[35]

- Stroke secondary to the occlusion of the MCA, within 6 hours of onset, in a patient not otherwise eligible for treatment with intravenous thrombolysis.
- Carefully selected ischemic stroke patients, presenting within 6 hours of symptom onset, who have a contraindication to receiving rtPA. Evidence is limited for use in this setting.

Intra-arterial thrombolysis should be performed by an interventional radiologist who is trained in this procedure, and in a stroke center where access to cerebral angiography is available. If a patient is eligible for treatment with IV tPA, intra-arterial thrombolysis should not be attempted as the primary treatment.

Endovascular Interventions. Endovascular interventions such as mechanical clot disruption and thrombus extraction are among the new wave of treatment techniques available for use in stroke patients with the etiology of arterial occlusion. These techniques are commonly studied as adjunct therapy to intravenous or intra-arterial thrombolysis.[48-50] Mechanical clot disruption has been shown to improve recanalization success,[48] but currently there is not enough evidence to support its routine use.[35] The only FDA-approved device for thrombus extraction is the MERCI device, used in the Mechanical Embolus Removal in Cerebral Embolism (MERCI) trial, where it was shown to rapidly re-open intracranial arteries.[50] The FDA has determined this device safe for use; however, like mechanical clot disruption techniques, the efficacy of thrombus extraction has not been established in clinical trials.[35] While endovascular interventions have shown potential in acute treatment of ischemic stroke, there are no current guidelines for their clinical use.

Future Directions

Recent advances in imaging and treatment modalities of acute stroke and TIA show great promise for improving patient outcomes. MRI technology has proved to be the most effective tool in the acute evaluation of stroke and TIA and will likely replace CT technology in the future. Imaging techniques will undoubtedly continue to evolve and shape the future of stroke care by allowing earlier and more accurate diagnosis of stroke and TIA.

Perfusion/penumbral imaging is particularly promising in defining the extent of tissue injury and determining which patients may benefit from reperfusion therapy. Future work in this area includes the validation of accuracy and clinical utility of perfusion imaging and standardization of imaging techniques.

Conclusion

Stroke and TIA represent a diagnostic challenge for EPs due to the time-sensitive nature of the pathophysiological process. Misdiagnosis or delayed diagnosis of stroke can lead to death or significant disability in patients, while early interventions and optimal medical management can have a positive impact on outcomes. New imaging techniques aim to identify acute cerebral hemorrhage and ischemia earlier, with greater accuracy, and in greater detail. MRI technology, along with its various pulsing sequences, has initiated a new era in stroke imaging with earlier and more sensitive detection of ischemia as well as enhanced characterization of the extent of tissue injury via perfusion/penumbral mapping. Stroke treatment has also experienced considerable advancement in the past decade with the use of intra-arterial thrombolysis and endovascular interventions, in addition to the extension of the time window for thrombolysis with rtPA.

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Physician CME Questions

81. In detection of intracerebral hemorrhage, GRE-MRI is:
    A. inferior to NCCT
    B. equivalent to NCCT in all areas
    C. equivalent to NCCT in detection of acute ICH and superior in detection of chronic hemorrhage and hemorrhagic transformation
    D. superior to NCCT in detection of acute ICH and equivalent in detection of chronic hemorrhage and hemorrhagic transformation

82. Which of the following is correct regarding the use of DWI-MRI in the evaluation of acute stroke?
    A. DWI should only be obtained acutely instead of NCCT if it does not unduly delay the administration of tPA in eligible patients.
    B. DWI can detect ischemic changes within minutes of the onset of ischemia.
    C. DWI has been shown to be the most sensitive and specific method for early detection of ischemia.
    D. All of the above are true.

83. What is the current role of perfusion imaging (CTP or MRP) in evaluation of acute stroke?
    A. Current guidelines do not recommend for or against the use of perfusion imaging in the evaluation of acute stroke.
    B. Perfusion imaging is an experimental imaging modality and its use has been abandoned in the evaluation of acute stroke.
    C. Perfusion imaging should be obtained in all stroke patients as perfusion-derived parameters are a critical factor in the decision to administer tPA.
    D. Diffusion/perfusion maps can be constructed using data solely from perfusion imaging.

84. Which of the following statements is true regarding the ability of MRA to detect cerebrovascular arterial lesions?
    A. MRA is better than CTA for detecting intracranial lesions.
    B. MRA and CTA are essentially equal in detecting extracranial lesions.
    C. MRA is less accurate than Doppler ultrasound in detecting extracranial lesions.
    D. Nonenhanced MRA is as accurate as gadolinium-enhanced MRA in detecting extracranial stenosis.

85. Ultrasound methods, such as carotid duplex ultrasound and transcranial Doppler, are not useful in the evaluation of an acute stroke.
    A. true
    B. false

86. Which of the following is the best imaging modality to evaluate an acute ischemic stroke?
    A. T1 MRI
    B. Non-contract CT
    C. Perfusion-weighted MRI
    D. Diffusion-weighted MRI

87. If access to MRI is not available, which of the following imaging modalities is most accurate in detecting acute ischemic stroke?
    A. NCCT
    B. CTP
    C. CTA-SI
    D. contrast-enhanced CT

88. Outpatient management is permitted for which of the following TIA patients according to current recommendations? Assume that neurological symptoms have resolved in all patients, and DWI-MRI did not show evidence of acute ischemia in any of the cases.
    A. a patient presenting within 4 hours of TIA with ABCD^2 score of 3 and reliable follow-up in less than 24 hours
    B. a patient presenting within 1 hour of TIA with ABCD^2 score of 2 and reliable follow-up within 48 hours
    C. an undomiciled patient presenting within 12 hours of TIA with ABCD^2 score of 1
    D. a patient presenting with ankle sprain, indicating that an episode of TIA occurred within the past 24 hours with an ABCD^2 score of 6. Patient has not been evaluated for this episode but is reliable for immediate follow-up.

89. Which of the following is a contraindication for administration of intravascular tPA in the 3- to 4.5-hour window, but not in the initial 3 hours?
    A. NIHSS of 22
    B. patient age of 75
    C. BP of 190/110
    D. use of oral anticoagulant with INR of 1.2

90. Which of the following statements regarding intra-arterial thrombolysis for acute ischemic stroke is *not true*?
    A. The only agent shown effective in a randomized trial is prourokinase.
    B. If both are available, intra-arterial thrombolysis is recommended as a primary treatment over intravenous rtPA.
    C. Intra-arterial thrombolysis can be used for both vertebral and basilar artery occlusions.
    D. Similar to intravenous rtPA, intra-arterial thrombolysis is associated with a 4 to 5 times increased rate of intracranial hemorrhage compared with control.

Corrections

In the February 28, 2011 issue, answer choice C in question 59 should read: The optic nerve should be measured at 3 mm behind the globe.

In the March 28, 2011 issue, the case presentation on page 93 should read, "An occlusion in the left PCA is visualized on MRA."

CME Answer Key

81. C; 82. D; 83. A ; 84. B; 85. B; 86. D; 87. C; 88. B; 89. D; 90. B

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Evaluation of Stroke and TIA: Part II

Comparison of Neuroimaging Techniques for Acute Stroke and TIA

Imaging Technique	Recommended Use	Main Characteristics	Notes
CT Imaging Techniques			
Non-contrast Computed Tomography (NCCT)	• Detection of hemorrhage • Detection of ischemia • Detection of intracranial malignancy or abscess	• Sensitivity (acute hemorrhage): +++ • Sensitivity (acute ischemia): + • Sensitivity (intracranial mass/abscess): ++ • Radiation exposure: Yes • IV contrast: No • Time to acquisition of images: ⧖ • Availability: +++ • Cost: $	• Reliable EP interpretations • Low detection rate of ischemia in the posterior circulation • Misses 1/3 of early ischemia (within 3 hours of onset)
CT Angiography (CTA)	Detection of intra- and extracranial vascular pathology	• Sensitivity (vascular pathology): +++ • Radiation exposure: Yes • IV contrast: Yes • Time to acquisition of images: ⧖ • Availability: +++ • Cost: $	
CTA Source Images (CTA-SI)	• Detection of intra- and extracranial vascular pathology • Detection of ischemia • Detection of cerebral perfusion abnormalities	• Sensitivity (vascular pathology): +++ • Sensitivity (acute ischemia): ++ • Sensitivity (perfusion abnormalities): +++ • Radiation exposure: Yes • IV contrast: Yes • Time to acquisition of images: ⧖ • Availability: +++ • Cost: $	• Obtained concurrently with CTA • Superior to NCCT in detection of early ischemia, and nearly as sensitive as DWI • May miss small foci of ischemia, especially in the posterior circulation
CT Perfusion (CTP)	Detection of cerebral perfusion abnormalities	• Sensitivity (perfusion abnormalities): ++ • Radiation exposure: Yes • IV contrast: Yes • Time to acquisition of images: ⧖ • Availability: ++ • Cost: $	Application of perfusion techniques to treatment and outcome is unclear
Multimodal CT (NCCT + CTA + CTP)	• Detection of hemorrhage • Detection of ischemia • Detection of intracranial malignancy or abscess • Detection of intra- and extracranial vascular pathology • Detection of cerebral perfusion abnormalities	• Sensitivity (acute hemorrhage): +++ • Sensitivity (acute ischemia): ++ • Sensitivity (intracranial mass/abscess): ++ • Sensitivity (vascular pathology): +++ • Sensitivity (perfusion abnormalities): +++ • Radiation exposure: Yes • IV contrast: Yes • Time to acquisition of images: ⧖⧖ • Availability: ++ • Cost: $	• Greater radiation exposure due to longer imaging time • May miss small foci of ischemia, especially in the posterior circulation

(*Continued*)

Comparison of Neuroimaging Techniques for Acute Stroke and TIA

Imaging Technique	Recommended Use	Main Characteristics	Notes
MR Imaging Techniques			
Magnetic Resonance Imaging (MRI)	• Detection of hemorrhage • Detection of ischemia • Detection of intracranial malignancy or abscess	• Sensitivity (acute hemorrhage): +++ • Sensitivity (acute ischemia): + • Sensitivity (intracranial mass/abscess): +++ • Radiation exposure: No • IV contrast: No • Time to acquisition of images: ⧖⧖ • Availability: ++ • Cost: $$$	Patient contraindications (e.g., pacemakers, metallic implants) and intolerance (claustrophobia) may interfere with image acquisition
Gradient Echo (GRE-MRI)	Detection of hemorrhage	• Sensitivity (acute hemorrhage): +++ • Radiation exposure: No • IV contrast: No • Time to acquisition of images: ⧖⧖⧖ • Availability: + • Cost: $$$	• Beware of patient contraindications and intolerance • More sensitive than NCCT in detection of hemorrhagic transformations, chronic hemorrhage, and microbleeds
Diffusion-Weighted Imaging (DWI-MRI)	Detection of ischemia	• Sensitivity (acute ischemia): +++ • Radiation exposure: No • IV contrast: No • Time to acquisition of images: ⧖⧖⧖ • Availability: + • Cost: $$$	• Beware of patient contraindications and intolerance • The most sensitive technique for the detection of early ischemia • Data can be used to construct diffusion/perfusion maps
Perfusion-Weighted Imaging (PWI-MRI)	Detection of cerebral perfusion abnormalities	• Sensitivity (perfusion abnormalities): +++ • Radiation exposure: No • IV contrast: Yes • Time to acquisition of images: ⧖⧖⧖ • Availability: + • Cost: $$$	• Beware of patient contraindications and intolerance • Data can be used to construct diffusion/perfusion maps • Application of perfusion techniques to treatment and outcome is unclear
MR Angiography (MRA)	Detection of intra- and extracranial vascular pathology	• Sensitivity (vascular pathology): +++ • Radiation exposure: No • IV contrast: Optional • Time to acquisition of images: ⧖⧖⧖ • Availability: + • Cost: $$$	• Beware of patient contraindications and intolerance • Use of IV contrast is optional • Slightly lower sensitivity than CTA in detecting intracranial lesions

(*Continued*)

Comparison of Neuroimaging Techniques for Acute Stroke and TIA (continued)

Imaging Technique	Recommended Use	Main Characteristics	Notes
Ultrasound Techniques			
Carotid Duplex Ultrasound & Transcranial Doppler	Detection of intra- and extracranial vascular pathology	• Sensitivity (vascular pathology): + • Radiation exposure: No • IV contrast: No • Time to acquisition of images: ⧖⧖⧖ • Availability: ++ • Cost: $	• Operator dependence • Requires availability of experienced ultrasonographers in the acute setting

Brain Imaging with Conventional MRI Sequences

	Water and CSF	Brain	Blood (acute < 6 h)	Ischemia (compared to nonischemic areas)
T1 images	Black	White matter brighter than gray matter	Gray	Darker gray
T2 images	White	Gray matter brighter than white matter	Light gray	Lighter gray
Spin-density (proton density) images	Dark gray	Gray matter brighter than white matter	Dark gray	Darker gray

Recommended Guidelines for Treating Elevated BP in Spontaneous ICH

Blood Pressure Management in ICH Patients

- If SBP is > 200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 min.
- If SBP is > 180 mm Hg or MAP is > 130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure ≥ 60 mm Hg.
- If SBP is > 180 mm Hg or MAP is > 130 mm Hg and there is no evidence of elevated ICP, then consider a modest reduction of BP (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically re-examine the patient every 15 min.

Calculating the ABCD2 Score

Age	
≥ 60 years	1 point
< 60 years	0 points
Blood Pressure	
Systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg	1 point
Systolic < 140 mmHg and diastolic < 90 mmHg	0 points
Clinical Features	
Unilateral weakness	2 points
Isolated speech disturbance	1 point
Other	0 points
Duration of TIA Symptoms	
≥ 60 minutes	2 points
10 to 59 minutes	1 point
< 10 minutes	0 points
Diabetes	
Present	1 point
Absent	0 points

Supplement to *Emergency Medicine Reports*, April 11, 2011: "Emergency Department Evaluation of Stroke and TIA: Beyond the CT Scan. Part II." *Authors:* **Bentley J. Bobrow, MD, FACEP,** Clinical Associate Professor, Emergency Medicine Department, Maricopa Medical Center, Phoenix, AZ; Medical Director, Bureau of EMS and Trauma System, Arizona Department of Health Services, Phoenix; and **Shadi Rafael**, Medical Student, University of Arizona College of Medicine, Tucson.
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