Ischemic Stroke

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KEYWORDS

• Ischemia • Infarction • Stroke imaging • Penumbra
• Perfusion

Acute ischemic stroke affects more than 659,000 Americans each year. If detected and treated early, accepted and emerging therapies have the ability to dramatically improve patient outcome. The goal of stroke imaging is to appropriately select patients for different types of therapeutic management in order to optimize outcome and minimize potential complications. To accomplish this, the radiologist has to evaluate each case and tailor an imaging protocol to fit the patient's needs and best answer the clinical question. This review outlines the routinely used, current neuroimaging techniques and their role in the evaluation of the acute stroke patient. In doing so, the ability of computed tomography (CT) and magnetic resonance (MR) imaging to adequately evaluate the infarcted brain parenchyma, the cerebral vasculature, and the ischemic, but potentially viable tissue, often referred to as the "ischemic penumbra," is compared. The authors outline an imaging algorithm that has been employed at their institution, and briefly review endovascular therapies that can be used in specific patients for stroke treatment.

IMAGING OF THE BRAIN PARENCHYMA

In the setting of acute ischemic stroke, both CT and MR imaging can be used to evaluate the cerebral parenchyma. The goals of both modalities are similar: (1) to exclude the presence of hemorrhage and mimics of stroke such as infection, inflammation, and neoplasm (among other entities), and (2) to detect and quantify infarcted tissue.

Imaging the Brain Parenchyma with CT

CT offers several practical advantages to MR imaging in the emergency setting. CT scanners are more widely available and patients can be brought to and from the scanner with minimal delay. Compared with MR imaging, CT requires much less prescreening; only contrast allergies and renal function need to be assessed. Furthermore, metallic equipment can safely accompany the patient in the CT scanner, allowing for easier monitoring of potentially unstable acute stroke patients.

Exclusion of hemorrhage

The presence of intracranial hemorrhage is an absolute contraindication to the administration of intravenous recombinant tissue plasminogen activator (rtPA), the only therapy with proven clinical benefit for the treatment of acute infarction. Noncontrast CT (NCCT) has long been the gold standard for detecting the presence of intracranial hemorrhage based on data from early CT scanners and practical experience.[1,2] A negative NCCT is required before the administration of rtPA according to guidelines established in 1995 by the National Institute for Neurologic Diseases and Stroke (NINDS) trial.[3,4]

Detection of infarcted tissue

Tissue that appears hypodense on NCCT is usually irreversibly infarcted, and likely represents all or part of the infarct core (discussed in subsequent sections). More subtle signs of cerebral ischemia may be detected on NCCT within a few hours of symptom onset. These signs have been well described in the literature and include the hyperdense vessel sign, the insular ribbon sign, obscuration of the lentiform nucleus, blurring of gray-white matter differentiation, and sulcal effacement (**Fig. 1**). Although well described, accurate detection and quantification of these signs remain highly reader dependent.

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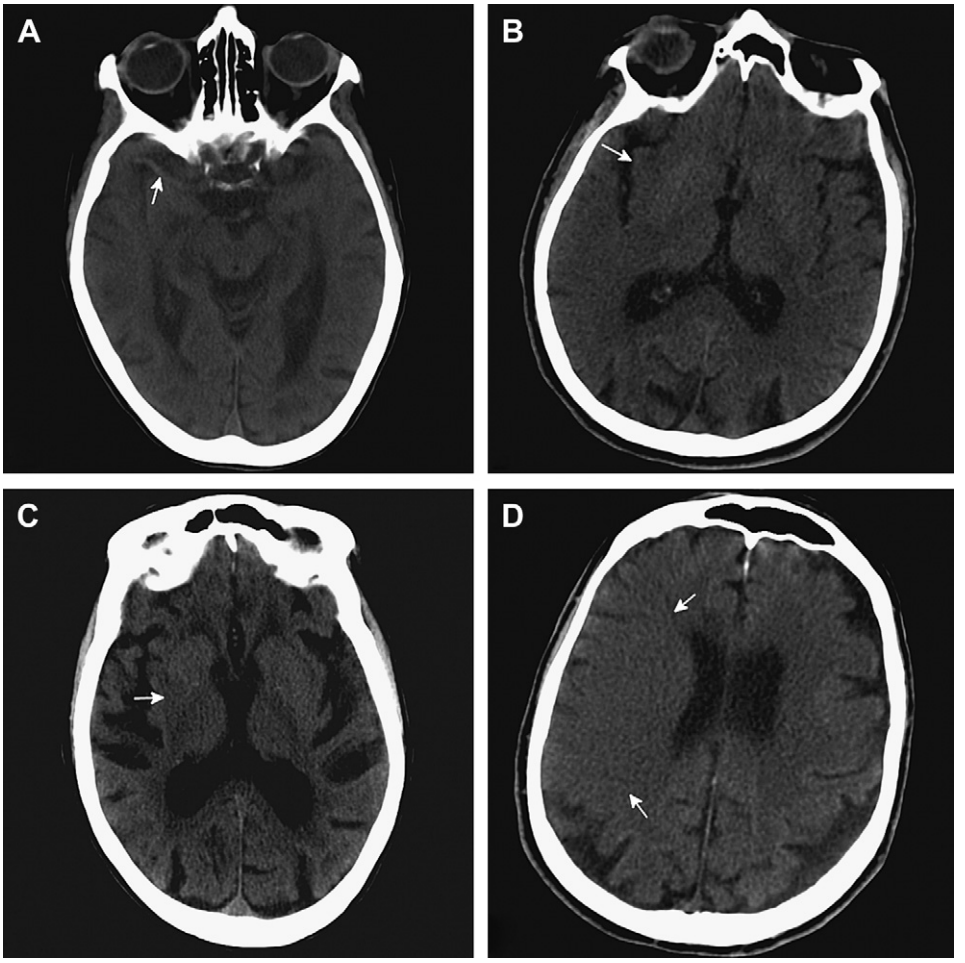

Fig. 1. Early signs (<6 hours) of cerebral infarction on noncontrast head CT. High density in the proximal middle cerebral artery (MCA) is thought to represent an acute thrombus lodged in the middle cerebral artery, and is referred to as the "hyperdense MCA sign" (*arrow* in *A*). The presence of edema in the distribution of the lenticulostriate arteries produces loss of the normal striated appearance of the insular cortex or "insular ribbon sign" (*arrow* in *B*) and local hypoattenuation in the basal ganglia, or "obscuration of the lentiform nuclei" (*arrow* in *C*). Loss of gray white matter differentiation and sulcal effacement (region between the 2 *arrows* in *D*) indicate diffuse cerebral swelling and, of the above signs, carry the poorest clinical prognosis.

Detecting signs of early ischemia on NCCT is influenced by several factors including the severity of the infarct, as measured by clinical examination and National Institutes of Health Stroke Scale (NIHSS) (**Table 1**), and the time between symptom onset and imaging.[5] The detection rate for signs of early ischemia within the 3-hour time window is 67% or less in most trials,[6–8] and may be as low as 31%.[5] Sensitivity is improved, up to 71%, by using narrow window width and center level settings (8 HU and 32 HU, respectively) to accentuate the contrast between normal and edematous tissue (**Fig. 2**).[9] The rate of detection increases to approximately 82% at 6 hours, which is outside the therapeutic window for intravenous rtPA.[10]

Quantifying the extent of infarction is also subject to great interreader variability. Specifically, when asked to determine if ischemic changes on NCCT involve greater than one-third of the middle cerebral artery (MCA) territory, even experienced clinicians show only 39% agreement.[7] In response, the Alberta Stroke Program Early CT Score (ASPECTS) was developed in 2001 to quantify acute ischemia on NCCT images by using a 10-point topographic scoring system (**Fig. 3**).[11] ASPECTS increased interreader reliability by up to 71% to 89%, and correlated well with functional outcome and risk of symptomatic intracranial hemorrhage (sensitivity/specificity 78%/96% and 90%/62%).[12] Despite this significant improvement,

Table 1
The National Institutes of Health (NIH) Stroke Scale

1a. Level of Consciousness	0 = Alert 1 = Not alert 2 = Not alert 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic
1b. LOC Questions: The patient is asked the month and his/her age	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the nonparetic hand	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2. Best Gaze: Only horizontal eye movements will be tested	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4. Facial Palsy:	0 = Normal 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis
5. Motor Arm: 5a. Left Arm 5b. Right Arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity; limb falls 4 = No movement UN = Amputation or joint fusion, explain:_____
6. Motor Leg: 6a. Left Leg 6b. Right Leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement UN = Amputation or joint fusion, explain:_____
7. Limb Ataxia:	0 = Absent 1 = Present in one limb 2 = Present in two limbs UN = Amputation or joint fusion, explain:_____
8. Sensory:	0 = Normal 1 = Mild to moderate sensory loss 2 = Severe to total sensory loss
9. Best Language:	0 = No aphasia; normal 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia
10. Dysarthria:	0 = Normal 1 = Mild to moderate dysarthria 2 = Severe dysarthria UN = Intubated or other physical barrier, explain:_____
11. Extinction and Inattention (formerly Neglect):	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention

The NIH Stroke Scale is a standardized method used by physicians and other health care professionals to measure the level of impairment caused by a stroke. The level of stroke severity as measured by this scoring system is: 0 = no stroke; 1–4 = minor stroke; 5–15 = moderate stroke; 15–20 = moderate/severe stroke; 21–42 = severe stroke.

ASPECTS is based on evaluating specific structures on 2 axial CT slices, making the system highly dependent on the imaging plane. More recently, the "ABC/2" method has been used to rapidly and accurately calculate the volume of infarcted tissue (**Fig. 4**).[13] Although originally described in MR, the technique, which measures lesions in 3 perpendicular axes, can by applied to both CT and MR, is independent of the imaging plane, and has shown high intrarater and interrater reliability (71%–99%).[13]

The importance of detecting and quantifying these early signs of infarction was demonstrated in the European Cooperative Acute Stroke Studies (ECASS I and II), where patients with large infarcts and early swelling were shown to have an increased incidence of hemorrhage and poor outcome following rtPA therapy.[3,14] Despite

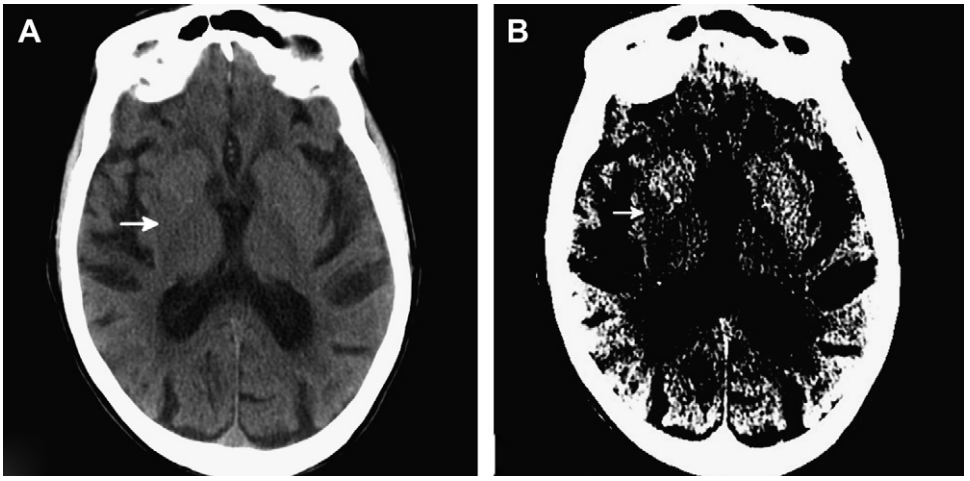

Fig. 2. Window level setting in stroke. Asymmetric low attenuation within the right posterior putamen (*arrows* in *A* and *B*) is subtle using standard brain window width and center level settings (*A*) (level 35, window 100), but becomes much more conspicuous with lower center level and narrower window width (*B*) (level 8, window 32).

some controversy,[5,15] these findings have resulted in the current consensus among stroke experts that the criteria for withholding rtPA in the first 3 hours after symptom onset include hemorrhage or definite signs of ischemia that exceed one-third of the MCA territory (correlating roughly to an ASPECTS score <7 and an ABC/2 volume >100 cm^3).[13,16] The recently published ECASS III trial indicates that this time window may now safely be increased to 4.5 hours.[17]

Imaging the Brain Parenchyma with MR Imaging

MR imaging with its multiple sequences provides excellent evaluation of the brain parenchyma for

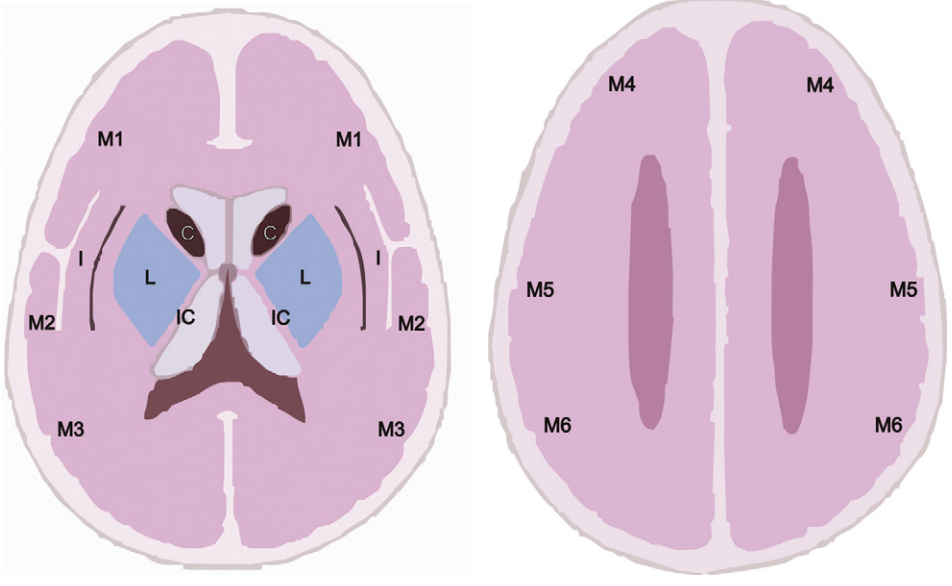

Fig. 3. ASPECTS Schematic. The ASPECTS scoring system is based on assessing 10 distinct regions of the MCA distribution on 2 axial slices. Once slice is centered at the level of the basal ganglia and thalami (*left*). Another slice is centered at the level of the centrum semiovale (*right*). Each demarcated region accounts for 1 point in the ASPECTS system: M1, M2, M3, M4, M5, M6, the insula (I), the caudate (C), the lentiform nucleus (L), and the internal capsule (IC). For each area involved by ischemia, 1 point is subtracted from a total score of 10 on each side. A sharp increase in dependent or fatal outcomes occurs with ASPECTS of 7 or less, corresponding roughly with an infarct involving greater than one-third of the MCA territory.

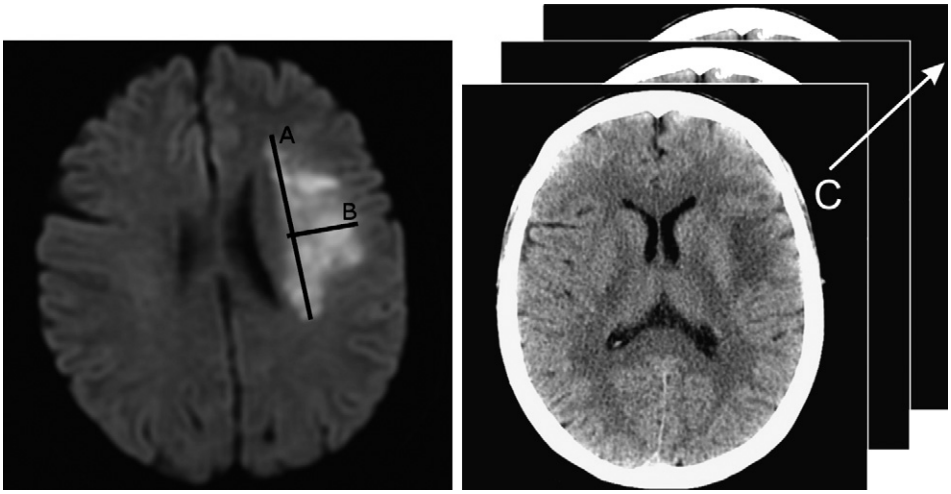

Fig. 4. ABC/2. The ABC/2 formula produces rapid and easy clinical assessment by correlating the region of infarction to the volume of an ellipsoid. The region of abnormal signal intensity (DWI, *left*) or reduced attenuation (CT, *right*) can be measured via 3 multiplanar, perpendicular axes. A and B are measured on the axial slice with the largest region of involvement (DWI, *left*). C is calculated from the number of axial slices the abnormality appears on, multiplied by the slice thickness (CT, *right*). A, B, and C are then multiplied, and the product is divided by 2 for the volume of infarcted tissue. A lesion between 70 and 100 cm^3 roughly correlates with one-third of the MCA territory and implies a poor prognosis.

stroke and its many mimics. MR imaging is also becoming widely available and can be found in the emergency rooms of some hospitals. Despite this, the previously mentioned practical considerations, including need for more extensive patient screening and incompatibility with routine patient monitoring equipment, remain the largest limitation for the use of MR imaging as the first-line imaging modality in acute stroke.

Exclusion of hemorrhage

The sensitivity of MR imaging for the detection of hemorrhage is primarily dependent on the age of the hemorrhage and the sequences used (**Table 2**). In the first 6 hours (the time frame that is critical for the treatment of acute ischemia), hemorrhage is mostly composed of oxyhemoglobin, with deoxyhemoglobin occurring in increasing amounts along the periphery (**Fig. 5**). Because oxyhemoglobin is isointense to the brain parenchyma on T1, hyperintense on T2, and diamagnetic, it may be overlooked on T1, T2, and gradient echo (GRE) sequences, particularly near cerebrospinal fluid (CSF) spaces. Deoxyhemoglobin may also be subtle on conventional sequences, as it is isointense on T1- and hypointense on T2-weighted sequences; however, its paramagnetism and resultant T2* effect make it conspicuous on GRE sequences. Although the high protein content of oxyhemoglobin makes it detectable in the subarachnoid space on fluid-attenuated inversion recovery (FLAIR) sequences, the appearance is nonspecific and can be mimicked by several pathologic and nonpathologic conditions, including flow artifact, meningitis, leptomeningeal metastases, oxygen therapy, and propofol administration.[18,19] These potential pitfalls continue to limit definitive exclusion of hemorrhage on MR imaging alone.

As any known prior intracranial hemorrhage is an absolute contraindication to intravenous rtPA therapy, the relatively common presence of chronic microhemorrhages has raised appropriate concern about intravenous rtPA administration in patients in whom they are seen. Chronic microhemorrhages can be defined as homogeneous rounded areas of signal loss that measure less than 5 mm in diameter without surrounding edema on GRE sequences. Recent studies have found no increased risk of hemorrhagic conversion of acute ischemic stroke treated with thrombolytic therapy in patients with up to 10 microhemorrhages detected on routine GRE sequences.[20,21] The risk in patients with more than 10 microhemorrhages remains undetermined.

Detection of infarcted or ischemic tissues

MR diffusion-weighted imaging (DWI) is the single most accurate method for detecting acute ischemia. DWI is based on the principle that the random (brownian) motion of water molecules in

Table 2
Stages of hemorrhage on MR and CT

Stage	Time Course	CT	T1	T2	Gradient Echo	Mass Effect	Components
Hyperacute	<6 h	High density	Low intensity	High intensity with peripheral low intensity	Centrally isointense, peripherally hypointense	+++	High protein, central oxyhemoglobin, peripheral deoxyhemoglobin
Acute	≈ 8–72 h	High density	Isointense to low intensity	Low intensity	Hypointense centrally and peripherally	+++	High protein, deoxyhemoglobin
Early subacute	≈ 3 d to 1 wk	High density	High intensity	Low intensity	Hypointense centrally and peripherally	+++/++	High protein, intracellular methemoglobin
Late subacute	≈ 1 wk to months	Isodense	High Intensity	High intensity with rim of low intensity	Isointense	±	Diluted protein, extracellular methemoglobin
Chronic	≈ months to years	Low density	Low intensity	Low intensity	Hypointense	-	Protein absorbed, hemosiderin

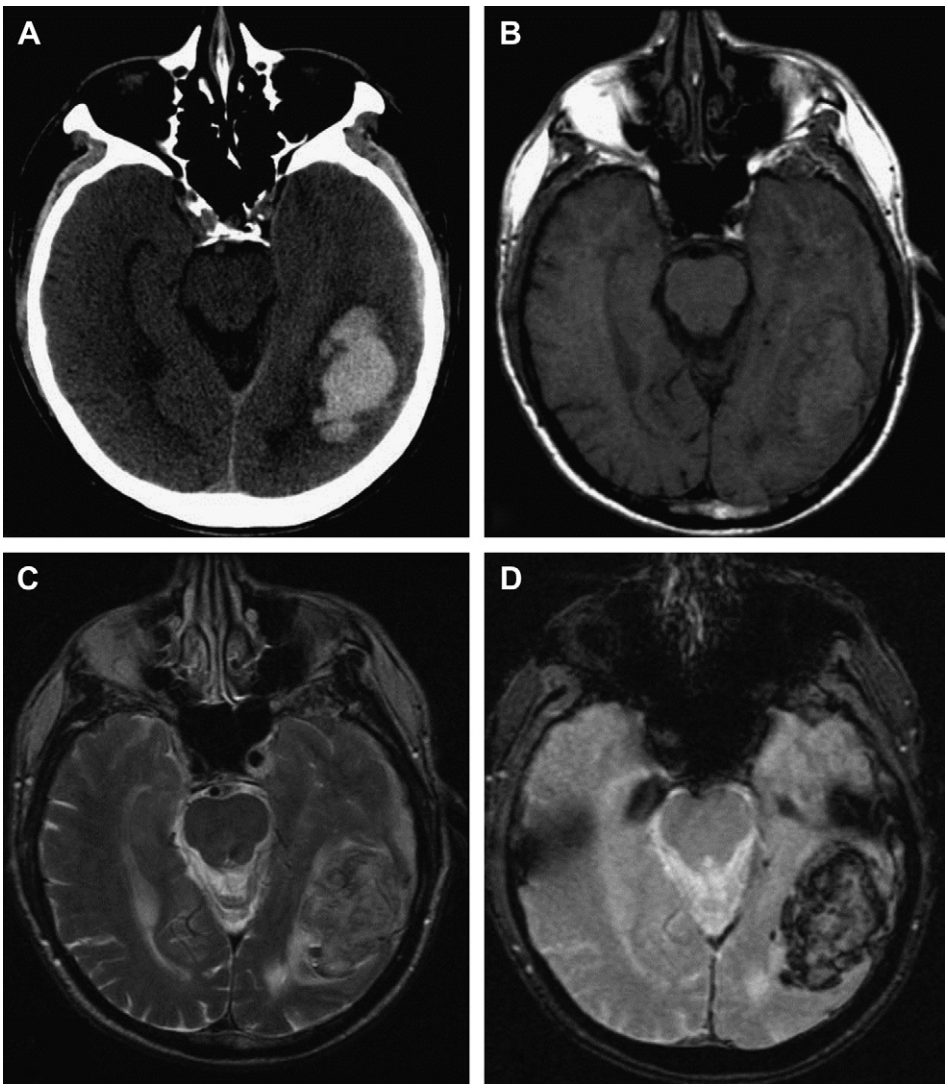

Fig. 5. Hyperacute (<6 hours) hemorrhage on CT and MR imaging. Hyperacute hemorrhage is hyperdense on non-contrast CT (*A*), isointense to the surrounding brain parenchyma on T1-weighted image (*B*), hyperintense to surrounding brain parenchyma on T2 (*C*), and demonstrates susceptibility artifact in increasing amounts along the periphery of the hemorrhage on gradient echo sequences (*D*), as oxyhemoglobin changes to deoxyhemoglobin.

living tissues can be quantitatively measured. Following application of equal and opposite strong gradient pulses combined with a spin-echo, echo-planar pulse sequence, loss of tissue signal is proportional to the rate of water diffusion. In the setting of acute ischemia, failure of the energy-dependent Na^+/K^+ transporter in neuronal and glial cells results in increased intracellular Na^+ and net translocation of water to the intracellular space. Intracellular water motion is relatively restricted by the presence of cell membranes and by the breakdown of organelles. Resultant cell swelling compresses the extracellular space, leading to more restricted movement of protons in that space as well. This decreased diffusion results in hyperintense signal on DW images that can be reliably detected within the first 30 minutes of stroke symptom onset, at a time when other MR imaging sequences and CT remain negative.

Contrast on DW images is exponentially related to differences in diffusion and linearly related to underlying T2 signal. To remove the T2 contrast,

a map of apparent diffusion coefficient (ADC) values is created by obtaining 2 image sets, one with a very low b value and one with b = 1,000 s/mm^2. By plotting the natural logarithm of the signal intensity versus b for these 2 b values, the ADC can be determined from the slope of this line. Alternatively, the DWI can be divided by the echoplanar spin-echo (SE) T2 image (or low b value image), to give an "exponential image" (EXP), the signal intensity of which is exponentially related to the apparent diffusion coefficient.[19] A DWI hyperintense lesion with truly restricted diffusion will be dark on ADC maps and bright on EXP images, whereas a lesion that is hyperintense on DWI due to the T2 component ("T2 shine-through") but has elevated diffusion will appear bright on ADC and dark on EXP images.

The high sensitivity and specificity of DWI is invaluable in reliably detecting the presence of and evaluating the extent of infarcted tissue. Reported sensitivities range from 88% to 100%, and reported specificities range from 86% to 100%.[3,22,23] Infarctions not identified on DWI (false negatives) are usually very small and located in the brainstem, deep gray nuclei, or cortex.[24] False-positive hyperintense DWI signal may result from T2 shine-through of subacute or early chronic infarctions, an error that is easily avoided by interpreting the DWI images in combination with ADC maps or exponential images. It is also well known that several nonischemic conditions can produce restricted diffusion, mimicking acute infarction on DW, ADC, and EXP imaging (**Table 3**). When reviewed in conjunction with conventional MR images and clinical history, these lesions can usually be distinguished from acute infarctions.[20] Reversible restricted diffusion (abnormal on initial DW, ADC, and EXP images, but normal on follow-up images) is very rare, but can occur more often with very early reperfusion, usually

Table 3
Nonischemic conditions that may cause restricted diffusion on MR imaging (hyperintense on DWI, hypointense on ADC)

Condition	Cause
Mass Lesions	
Epidermoid mass	Hypercellular tumor
Lymphoma	Hypercellular tumor
Glioblastoma	Hypercellular tumor
Medulloblastoma	Hypercellular tumor
Traumatic	
Diffuse axonal injury (most cases)	Cytotoxic edema
Hemorrhage (oxyhemoglobin)	Intracellular, high protein content
Hemorrhage (extracellular methemoglobin)	High protein content
Infectious	
Abscess or pyogenic infection	Increased viscosity
Herpes encephalitis	Cytotoxic edema
Creutzfeldt-Jakob syndrome	Spongiform change
Inflammatory	
Multiple sclerosis (a few acute lesions)	Myelin vacuolization
Other	
Hemiplegic migraine	Na^+/K^+ adenosine triphosphatase (ATPase) activity decrease, spreading depression
Seizure activity	Na^+/K^+ ATPase activity decrease
Transient global amnesia	Unknown,? ischemia
Heroin leukoencaphalopathy	Myelin vacuolization
Flagyl	? Axonal swelling limiting extracellular space
Hypoglycemia	Na^+/K^+ ATPase activity decrease

following intravenous and/or intra-arterial thrombolysis. Despite these potential pitfalls, DWI has emerged as the most sensitive and specific imaging technique for detecting acute infarction and as the gold standard for delineating infarction core.[16] The size of the DWI lesion may also have a role in predicting patient outcome. In particular, at least 2 studies have demonstrated that large initial DWI volumes predict poor outcome and increased risk of intracranial hemorrhage.[25,26] As a result, those patients with an initial DWI lesion volume of greater than one-third of the MCA territory or greater than 100 cm^3 are typically excluded from acute stroke trials.

Other MR imaging sequences can support the diagnosis of and help estimate the age of infarction. The MR correlates of the CT "hyperdense vessel sign" are focal vessel hyperintensity on FLAIR, vascular susceptibility artifact on GRE, and loss of a normal flow void on T2 sequences. Of these, vessel hyperintensity on FLAIR images is the most sensitive, with one study showing detection rates comparable to MR angiography (MRA) in both middle and posterior cerebral arteries.[27] Effacement of sulci, cisterns, and ventricles due to mild swelling can be seen within the first few hours after stroke symptom onset, prior to any parenchymal signal abnormality.[28] Edema associated with infarction presents earliest on FLAIR sequences, but still only achieves a sensitivity of 29% in the first 6 hours after stroke onset.[29] By 8 hours, hyperintense signal develops on T2-weighted images and by 16 hours, low signal intensity is noted on T1-weighted images (**Table 4**).[28] With this approximate guideline in mind, for patients in whom the time of stroke onset is not known (eg, a "wake-up-stroke") and in whom MR imaging confirms an infarct on DWI and ADC, but shows no or minimal FLAIR hyperintense signal, the time of onset is likely less than 6 hours (**Fig. 6**). Although these patients cannot receive rtPA by NINDS criteria, ongoing research is investigating whether they may benefit from interventional therapies.

IMAGING OF THE CEREBRAL VASCULATURE

Vascular imaging in the acute ischemic stroke patient most commonly extends from the aortic arch to the cranial vertex. Evaluation of the intracranial circulation is performed to identify and characterize the vascular lesion, and to quantify the extent of collateral flow. In general, vascular lesions in the proximal, large vessels result in the largest infarcts with the greatest likelihood of hemorrhagic transformation, and the greatest potential benefit from neuroendovascular intervention. In these cases, the presence and extent of collateral vessels helps to determine the territory at risk. In the absence of a visible occlusion, infarcts may be caused by lesions in small arteries that cannot be imaged, or by an embolus in a large proximal artery that has broken up spontaneously. In general, such patients have relatively favorable outcomes.[22]

Evaluation of the extracranial circulation is mainly performed to identify and characterize a potentially thrombotic or embolic source and to help determine whether treatment should be medical or surgical. Correctly characterizing a diseased vessel segment is critical for patient care, as occlusions are typically treated pharmacologically, whereas endarterectomy or stent placement is indicated for symptomatic patients with greater than 70% stenosis. Diagnosis of potentially treatable diseases, such as vasculitis, may benefit from cross-sectional imaging that adequately evaluates the vessel lumen, wall, and adjacent soft tissues. Patients with a history of atrial fibrillation may benefit from extended vascular imaging to exclude the presence of a left atrial or ventricular thrombus.

Although digital subtraction angiography (DSA) remains the reference standard for vascular imaging, it is an invasive procedure that carries risks, is costly, and is time-consuming. For these reasons, noninvasive techniques have replaced DSA in the initial, emergent evaluation of the acute stroke patient. The techniques, advantages, and disadvantages of the 2 most common noninvasive vascular imaging modalities, CT and MRA, are now discussed.

CT Angiography

Technique

CTA techniques vary largely by institution. At the authors' institution, CTA is typically performed by injecting 80 mL of intravenous contrast at 3.5 to 5 mL/s through a power injector with a saline chaser. Image acquisition is synchronized to the peak arterial enhancement by a bolus-triggering method. Images are acquired with a maximally overlapping pitch and a thin overlapping slice reconstruction (1.25 mm thick by 0.625 interval), and are reconstructed with a soft tissue algorithm for improved 3-dimensional (3D) reformatting. Postprocessing is essential for complete vessel analysis and includes thick section maximum intensity projections (MIPs) created at the scanner, and 3D volume rendered reformatted images, which are performed in time for final review.

Table 4
Time course of infarction on MR imaging

Stage	DWI	ADC	EXP	T1	T2/FLAIR
Hyperacute (0–6 h)	Hyperintense	Hypointense	Hyperintense	Isointense—perhaps some loss of sulci	Isointense
Acute (6 h to 4 d)	Hyperintense	Hypointense	Hyperintense	Iso- to hypointense—mass effect	Hyperintense (FLAIR becomes reliably hyperintense slightly before T2)
Subacute (4–14 d)	Hyperintense due to T2 shine-through	Iso- to hyperintense (pseudonormalization)	Iso- to hypointense	Hypointense	Hyperintense
Chronic	Hyperintense due to T2 shine-through	Hyperintense (encephalomalacia)	Hypointense	Smaller area of hypointense signal	Hyperintense

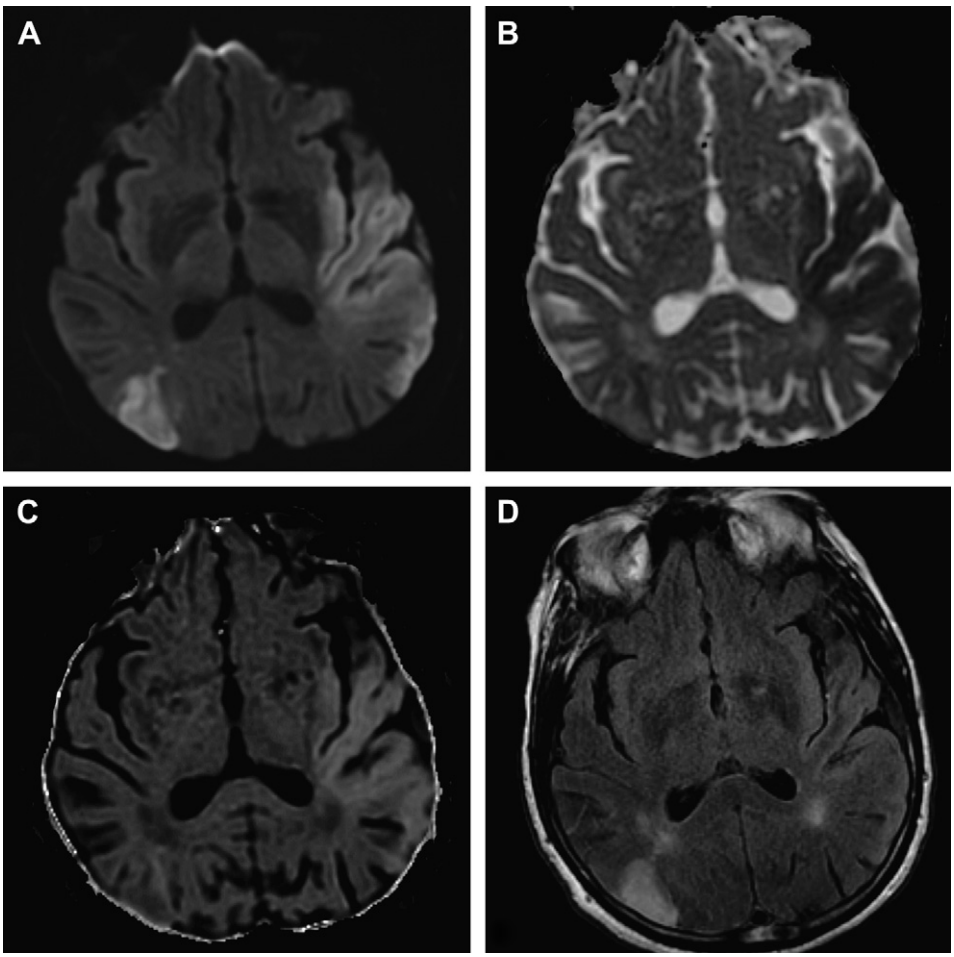

Fig. 6. Estimating the age of infarction. A 73-year-old man presented 3 hours after sudden onset of aphasia. Hyperintense DWI signal within the left posterior insula and temporal lobe (*A*) with corresponding low signal intensity on ADC maps (*B*), hyperintense signal on EXP (*C*), and only subtle hyperintense signal and edema on FLAIR (*D*) is consistent with a hyperacute (<6 hours) infarction, and is likely the cause of the patient's new onset deficit. A second, smaller infarction in the right parieto-occipital region is mostly hyperintense on DWI (*A*), isointense on ADC maps (*B*), isointense on EXP maps (*C*), and hyperintense on FLAIR (*D*), findings that are more consistent with a subacute timeframe (5–10 days), and was clinically silent.

Advantages

In addition to more widespread availability, CTA offers several practical benefits for vascular imaging in the acute stroke setting. Most CT scanners are capable of performing CTA immediately following NCCT. Once hemorrhage has been excluded, rtPA therapy can be initiated immediately without requiring personnel and equipment to be screened for safety. Modern multidetector CT scanners afford a short acquisition time, which decreases the incidence of motion-related artifacts and venous contamination. CTA uses a true intravascular contrast agent, and is therefore less susceptible to artifactual vessel narrowing caused by turbulent or slow flow on time-of-flight MRA images. In addition, CTA is not susceptible to the phase and susceptibility artifacts that may affect Gadolinium contrast-enhanced MRA (CE MRA). The spatial resolution of CTA is also approximately twice that of MRA.

Several studies evaluating the accuracy of CTA in the intracranial circulation have focused on the proximal large intracranial vessels, including the internal carotid arteries, and first and second segments of the anterior, middle and posterior cerebral arteries. In one study using DSA as the gold standard, CTA demonstrated 98.4% sensitivity and 98.1% specificity for detecting proximal

vessel acute occlusive thrombus.[23] In another study, DSA was significantly more sensitive than time-of-flight (TOF) MRA for both intracranial stenosis (98% vs 70%, $P<.001$) and occlusion (100% vs 87%, $P = .02$).[24] CTA MIPs increase conspicuity of vascular stenosis/occlusion in both proximal and distal vessels (**Fig. 7**); they are also the most accurate method for quantifying the degree of collateral circulation, which has shown an inverse correlation with the final infarct volume.[30]

For evaluation of the extracranial circulation, CTA is also generally preferred to MRA. Although controversial, several studies have demonstrated CTA to have the strongest correlation with DSA, citing better spatial resolution, less flow dependence, and the ability to demonstrate both luminal and extraluminal abnormalities that augment evaluation of vascular narrowing.[31–38] A 2004 meta-analysis pooled data from 28 studies comparing CTA with DSA, and found CTA to have 85% sensitivity and 93% specificity for detection of a 70% to 99% stenosis, and 97% sensitivity and 99% specificity for detecting an occlusion.[39] Studies comparing CTA and MRA for carotid and vertebral artery dissection vary widely by technique. A recently published meta-analysis found both modalities to have similar correlation with DSA (sensitivities and specificities ranging from 51% to 100% and 67% to 100% for CTA, and 50% to

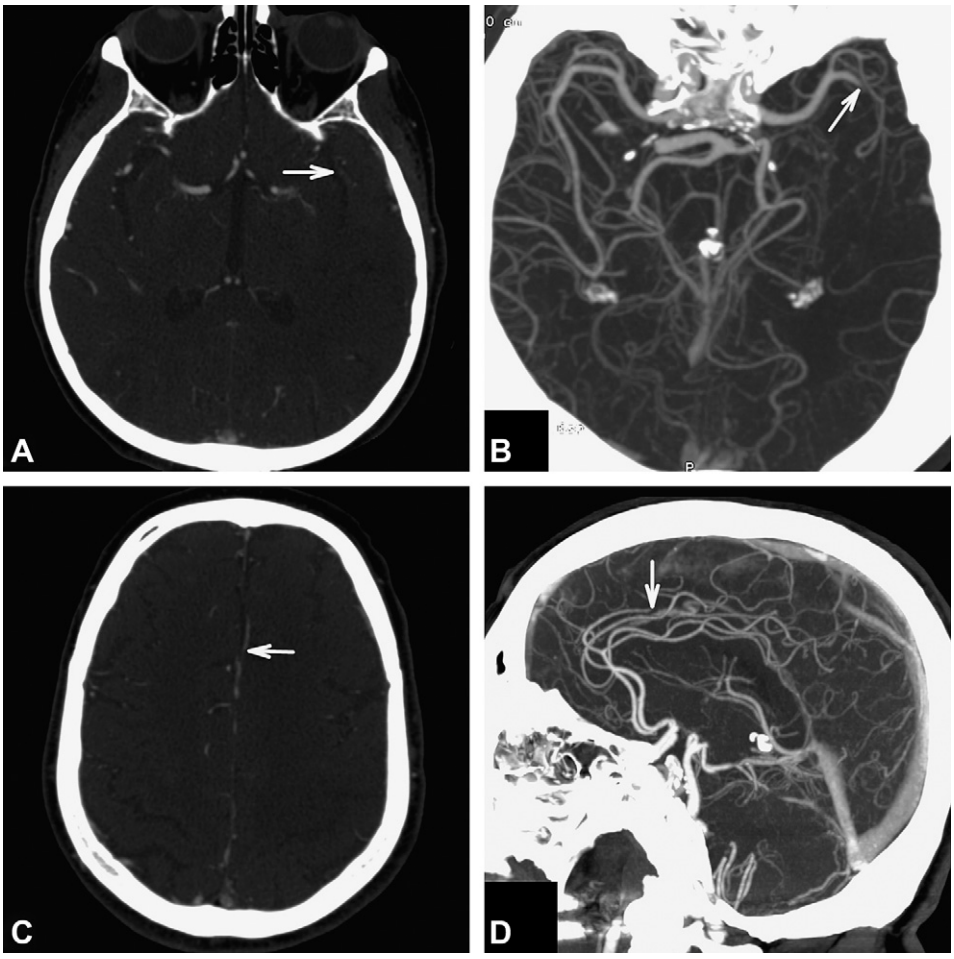

Fig. 7. Benefits of MIPs in vessel evaluation. Vessel occlusion or thrombus in the distal intracranial circulation is complicated by small vessel caliber and tortuosity. MIPs are created by "stacking" axial CT slices on top of one another and "windowing" to highlight areas of high radiodensity. The 3D volume can be used to evaluate a single, distal tortuous vessel along its length. A vessel occlusion in the left MCA superior division was oriented perpendicular to the axial CTA source images (*arrow* in *A*), making visualization difficult. The occlusion was clearly identified on the axial MIP as a vessel cutoff (*arrow* in *B*). In the same patient, a subtle left distal anterior cerebral artery occlusion was not prospectively visualized on the axial CTA source images (*arrow* in *C*), but was identified on the sagittal MIPs (*arrow* in *D*).

100% and 29% to 100% for MRA, respectively).[40] Despite this, certain limitations of MR imaging and MRA, including obscuration of mural hematoma by hyperintense signal from an adjacent occlusive thrombus, as well as lack of hyperintense signal within mural hematoma on T1-weighted images in early dissection, are overcome by CTA.[40,41]

CTA may also have a role in evaluation of the brain parenchyma in acute stroke patients. If imaging is appropriately timed to the contrast bolus, both the large vessels and the microvasculature become opacified and hypoperfused brain becomes visibly hypodense on CTA source images (CTA-SI). CTA-SIs increase the detection of acute ischemia,[42] and increase the utility of ASPECTS as compared with NCCT. On 4- and 16-detector row CT scanners, lesion volumes on CTA-SI correlate closely with those on DWI, and with the final infarct volume in patients who reperfuse, suggesting that they identify the infarct core.[43,44] However, although 4- and 16-detector row scanners allow the contrast bolus to achieve a "steady state" during which the microvasculature becomes opacified, newer 64 and higher detector row CT scanners can outpace the flow of contrast-opacified blood; consequently, CTA-SIs on these scanners show areas of hypodensity that are larger than the DWI abnormality and overestimate the final infarct size (Hu R. and colleagues, unpublished data, 2010).

Disadvantages

The main disadvantage of CTA is radiation exposure, which requires an additional dose of approximately 2.5 mSv for a CTA of the head, and 9.5 mSv for a CTA of the head and neck.[45] In the acute stroke setting, additional delayed-phase CTA may also be necessary for accurate image interpretation. For example, apparent vascular occlusions require delayed images to differentiate between true occlusion and delayed opacification due to slow flow. Furthermore, if the major venous sinuses are not adequately opacified and there is suspicion of venous infarction, delayed images of the head should be obtained to exclude venous sinus thrombosis. The most critical aspect of limiting radiation exposure in the acute stroke setting is active monitoring of image acquisition, and tailoring additional sequences to those that are necessary for accurate interpretation with the constant, conscious goal of minimizing the patient's overall radiation dose.

CTA also requires injection of iodine-based contrast material, which has the potential to exacerbate already impaired renal function and may trigger adverse allergic reactions. A recent review evaluated the incidence of contrast-induced nephropathy in patients receiving both CTA and CT perfusion (CTP) imaging for the evaluation of acute stroke. Of the 198 patients studied, none developed chronic kidney disease or required dialysis, and 2.9% experienced a significant increase in baseline creatinine values.[46] The risk of allergic reaction has decreased significantly with the now widespread use of low-osmolar nonionic contrast media, with a reported overall incidence of 0.15%, less than 0.03% of which require medical treatment.[47] Decisions about whether to proceed with intravenous contrast administration should be made with these data in mind, and in close consultation with the clinical team.

Interpretation of CTA can be limited by several artifacts that may result in partial or significant obscuration of adjacent arteries. Streak artifact commonly results from metallic hardware in the upper chest (pacemaker) or neck (dental hardware), from photon starvation between the shoulders, or from slow-flowing contrast material in the adjacent veins. Heavy atherosclerotic calcification may also produce streak artifact that can overestimate vessel stenosis and/or mimic an occlusion. In addition, CTA performed on 64-detector scanners[48] is susceptible to flow artifacts and misrepresentation of flow dynamics (eg, pseudodissection or pseudo-occlusion). Most of these artifacts can be accurately identified by an experienced reader. Targeted delayed imaging or correlation with another vascular imaging modality may also be helpful.

MR Angiography

Technique

MRA describes any of several MR imaging techniques used to depict arteries. In the setting of acute stroke, a typical protocol is a 3D TOF sequence through the circle of Willis, and a CE MRA or a 2-dimensional (2D) TOF sequence through the neck. TOF is a GRE technique that images vascular flow by repeatedly (with a short repetition time [TR]) applying a radiofrequency pulse to a given volume of tissue, perpendicular to the direction of blood flow. The short TR interval allows saturation of stationary tissue, while protons within flowing blood remain bright. Maximum flow signal is achieved when a totally new column of blood enters the slice every TR period. A saturation pulse placed superior to the volume of tissues eliminates venous contamination. TOF MRA is most commonly acquired from sequential axial slices (2D), or a single large volume (3D) depending on the coverage required and the range of flow velocities under examination. 2D TOF MRA is more sensitive to slow flow,

making it ideal for longer vessel segments with limited tortuosity (eg, neck vessels). 3D TOF MRA takes longer to perform and is less sensitive to slow flow, but has a relatively higher signal to noise ratio and higher spatial resolution, making it the better choice for small, tortuous vessels (eg, the intracranial vessels).

CE MRA of the neck is most commonly performed using a technique that is conceptually similar to that used for CTA. An intravenous injection of a short dense bolus of gadolinium is imaged on its first pass through the arterial system. In high concentrations, the gadolinium markedly shortens the T1 of the intermixed blood. The extremely short TR values ensure saturation of almost all stationary tissues and produce a high sensitivity to the gadolinium-enhanced blood. Images are typically acquired in the coronal plane and the peak of the contrast bolus is mapped to the center of k space.

Of note, phase-contrast MRA is another noncontrast technique that generates both magnitude and phase images, displaying blood vessel anatomy and direction of flow, respectively. The technique has some advantages over TOF MRA, including decreased sensitivity to some flow-related artifacts and superior background suppression; however, increased acquisition time and technical variability make it less useful in the acute stroke population, and it is not discussed further here.

Advantages

In the setting of acute stroke, TOF MRA techniques provide an invaluable imaging alternative for patients with renal insufficiency or intravenous contrast allergy. Although the sensitivity and specificity for detecting intracranial stenoses and occlusions is inferior to CTA (discussed in the section on CTA advantages), 3D TOF MRA still provides excellent evaluation of the proximal, large intracranial vessels, particularly when combined with additional sequences (DWI, vascular susceptibility signal on GRE, and FLAIR hyperintense vessel signal).

For evaluation of the extracranial vasculature, both CE MRA and 2D TOF techniques are comparable to CTA. A recent study compared both MRA techniques with CTA in the evaluation of greater than 70% carotid stenosis, and demonstrated an accuracy of 92.9% for 2D TOF MRA and 93.8% for CE MRA.[49] CE MRA is usually preferred because it performs better than 2D TOF MRA in evaluation of the proximal arch vessels, and the visualization of such findings as hairline occlusion, dissection, or tandem lesions, detection of which can have important implications for patient management.[50–52] TOF MRA is typically used for patients with renal failure and contrast allergies, and when direction of flow needs to be evaluated, such as suspected subclavian steal.

Disadvantages

Aside from the practical considerations inherent to the MR imaging technique, both TOF and CE MRA have technical limitations that reduce their specificity. In 2D TOF MRA, turbulent flow from stenotic vessel segments results in intravoxel dephasing, which appears as signal-intensity drop-out (or flow void).[53,54] Although this flow void correlates well with a stenosis of greater than 70%, on both CTA[49] and DSA[55] the exact percentage of narrowing cannot be measured. 3D TOF is less sensitive to slow flow and is vulnerable to saturation effects, which refer to a gradual loss of T1 signal caused by repeated excitation with radiofrequency pulses. Both of these factors contribute to poor visualization of the distal intracranial vessels on MRA, and therefore inability to assess the collateral circulation. CE MRA is highly technique dependent, and overestimation of carotid artery narrowing can result from several sources, including dephasing artifacts along the margin of the lumen (which become exaggerated in areas of tight narrowing) (**Fig. 8**), susceptibility artifacts from a dense bolus contrast injection, the signal-intensity threshold used to create the MIPs, and the section thickness causing partial volume averaging effect.[56–58]

CE MRA requires the administration of gadolinium, which has been associated with nephrogenic systemic fibrosis (NSF), a progressive fibrosing dermopathy. Although the exact pathophysiology of NSF is unclear, it is likely caused by a combination of decreased kidney function, presence of inflammation, and exposure to gadolinium-based contrast agents.[59,60] The highest reported incidence of NSF was 8.8% in patients whose glomerular filtration rate (GFR) was less than 15 mL/min, were not undergoing hemodialysis, and received high, nonstandard doses of gadolinium.[61] The incidence of NSF has disappeared with the now routine screening of renal function in at-risk patients prior to gadolinium administration.

EVALUATING TISSUE VIABILITY/PERFUSION IMAGING

Perfusion imaging techniques evaluate capillary, tissue-level circulation, which is beyond the resolution of traditional anatomic imaging. In general, both CT and MR perfusion techniques use rapid serial imaging to dynamically trace the wash-in and wash-out of a contrast bolus power injected into a peripheral vein through an intravenous catheter. In the setting of CT, the iodine-based contrast

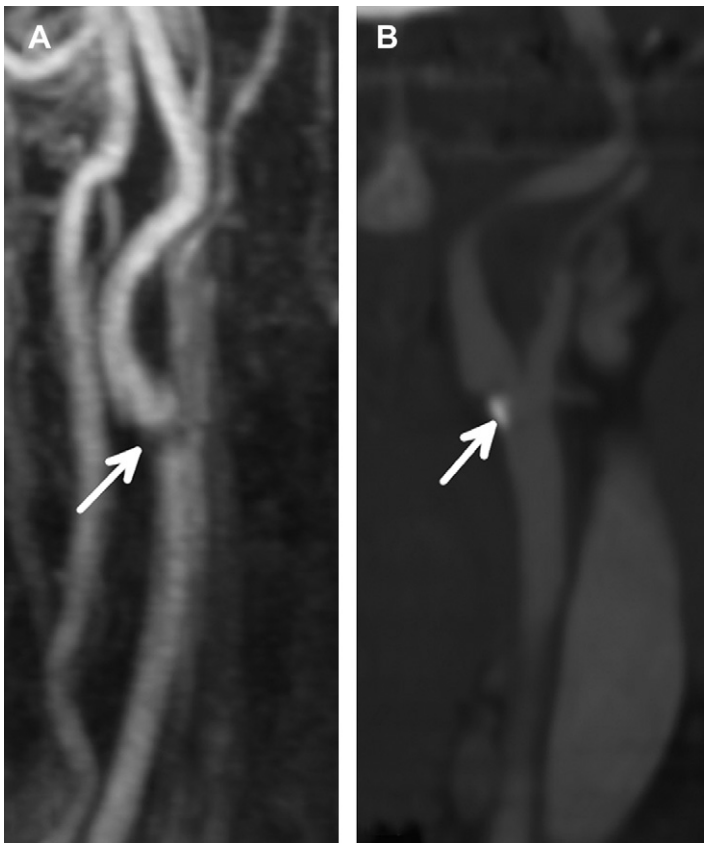

Fig. 8. MRA versus CTA. A 57-year-old woman with transient ischemic attack. Coronal gadolinium-enhanced MRA MIP (*A*) was slightly motion degraded, and loss of signal in the left distal common carotid artery (*arrow*) was thought to be compatible with a moderate to severe stenosis. CTA was recommended and CTA MIP (*B*) showed a corresponding focal calcification (*arrow*) with mild to moderate stenosis.

bolus causes a transient increase, then decrease in the density of the brain parenchyma over time. In the setting of MR imaging, the signal intensity of the brain parenchyma decreases, then increases over time because of susceptibility artifact on the T2* GRE echo planar images. These images are then analyzed by a computer and converted into contrast versus time curves, which can be used to estimate particular perfusion measurements in each part of the brain: mean transit time (MTT), cerebral blood volume (CBV), and cerebral blood flow (CBF).

MTT is measured in seconds and represents the average time required by a red blood cell to cross the capillary network. CBV is measured in milliliters per 100 g of brain tissue and reflects the blood pool content of each pixel. Knowledge of these 2 values can be used to calculate CBF according to the *central volume theorem*: CBF = CBV/MTT. CBF is measured in milliliters per 100 g of brain tissue per minute and reflects the amount of blood flowing through each pixel in 1 minute. Additional transit time measures used for MR imaging are time to peak (TTP) (which reflects the time it takes to reach maximal susceptibility effect) and Tmax (which is the time to peak of the deconvolved residue function).

Conceptually, CBF, CBV, and MTT reflect the following. Distal to an occlusion, cerebral perfusion pressure decreases, resulting in a heterogeneous reduction in CBF that is largely dependent on the local cerebral perfusion pressure and collateral flow. With mild reduction in CBF, compensatory vasodilation and capillary recruitment results in an increase in the amount of blood in each pixel (CBV) and a prolongation in the amount of time it takes for a red blood cell to cross the capillary network (MTT). In this tissue oxygen delivery is maintained, thereby preserving oxidative metabolism and neuronal function. In areas where CBF has decreased beyond the support of local autoregulatory mechanisms, microvascular collapse occurs, resulting in decreased CBV. In these areas oxygen delivery is impaired, leading within seconds to cessation of neuronal electrical activity, and within minutes to deterioration of the energy state and ion homeostasis.[62]

In practice, perfusion maps are most frequently interpreted by inspecting them for "lesions" representing abnormal CBV, CBF, or MTT. In this interpretation, the terms "infarct core" and "ischemic penumbra" are often used. The core, which often lies near the center of the ischemic region, is defined as the tissue that has been irreversibly damaged and is unlikely to survive regardless of therapeutic intervention. This tissue is represented by decreased CBV, severely decreased CBF, and increased MTT. The term "ischemic penumbra" is often used to describe a region of tissue that is threatened by ischemia, but may be saved by rapid reperfusion. This only moderately ischemic tissue often surrounds the ischemic core, where collateral vessels provide some degree of residual perfusion; this region typically has preserved or increased CBV, mildly decreased CBF, and increased MTT (**Fig. 9**). Discrimination between the infarct core and its surrounding potentially salvageable penumbra has been the focus of functional imaging over the past decade, spurred by the hope that patients with a large penumbra and small infarct core may benefit from thrombolysis well beyond the initial hours of stroke symptom onset. Since that time, there has been near-continuous debate over which imaging modality (MR or CT) is best suited to clinically make this distinction. A summary of CT and MR techniques for defining the infarct core and penumbra is provided in **Table 5**.

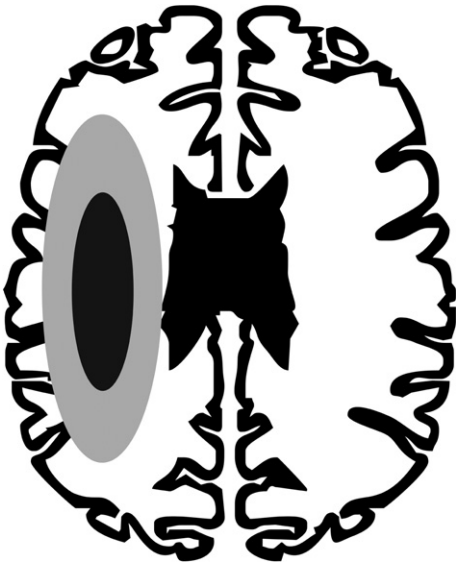

Fig. 9. Acute infarction. Within the right middle cerebral artery vascular territory infarction, the central, darker gray oval represents the infarct "core," or tissue that is irreversibly damaged. In practice, this region is best delineated by restricted diffusion. Hypodense regions on NCCT and CTA-SI (on 4- and 16-detector scanners) also depict infarct core. On perfusion imaging, this region is represented by severely decreased CBF, increased MTT, and decreased CBV. The peripheral lighter gray oval represents the "ischemic penumbra," tissue that is threatened by ischemia but may be saved by rapid reperfusion. In practice, this region is represented by mildly decreased CBF, increased MTT, and preserved or increased CBV.

CT Perfusion

Technique

CTP techniques vary largely by institution. At the authors' institution, CTP studies are performed on a 64-slice scanner. Two sequential 4-cm thick sections are selected, starting at the level of the basal ganglia on unenhanced CT. Following a 37-mL bolus contrast injection at 7 mL/s, cine CT scanning is initiated at 1 image/s for a duration of 45 seconds. After this, 5 sets of axial images are obtained every 15 seconds for an additional 75 seconds. The process is then repeated for the next section.

CTP data are analyzed at an imaging workstation equipped with commercially available software. Postprocessing involves placement of freehand-drawn regions of interest in an input artery (eg, the A1 segment of the anterior cerebral artery) and an input vein (eg, the torcula Herophili), for which contrast-enhancement curves are generated. CBV is calculated from the area under the curve in a parenchymal pixel divided by the area under the curve in an arterial pixel. Deconvolution analysis of arterial and tissue time attenuation curves is used to obtain the MTT. CBF is then calculated according to the central volume theorem (see equation given earlier). The software then generates color-coded CBF, CBV, and MTT maps.

Interpretation

On CTP, CBV maps are usually used to define the infarct core. Tissue that appears normal on CBV maps but abnormal in CBF or MTT maps is thought to represent the ischemic penumbra (**Fig. 10**). Several studies have validated the ability of CTP to distinguish between core and penumbra within and beyond the 3-hour time window, some by comparing perfusion parameters to the contralateral brain parenchyma,[63] to MR imaging (both MR perfusion [MRP][64] and DWI/FLAIR[65]), and to a combination of DWI and NIHSS.[66] At present, however, no large clinical trials have been successfully completed using only CTP to select patients for reperfusion therapy during the 3- to 9-hour time window. Smaller trials beyond the 3-hour time window have suggested that the most effective method to distinguish between

Table 5
Summary of CT and MR techniques for defining infarct core and penumbra

Modality	Infarct Core	Penumbra
CT	• Hypodensity reveals all or part of the infarct core • Specific, but not sensitive	• Subtle CT ischemic signs are not sensitive or specific

MR imaging	• DWI is the most sensitive and specific imaging marker
	• Core >100 cm^3 ≈ one-third of the MCA territory
	  • Poor patient prognosis
	  • Contraindication to thrombolysis
		• Cannot define

CTA	• CTA source images have been used to define the infarct core • Results are highly dependent on technique	• Cannot define
MRA	• Cannot define	• Cannot define

CTP	• Best estimated by low CBV
	• Threshold values have not been established
	• Less sensitive & specific than DWI
		• Tissue that is:
		  • Normal on CBV maps
		  • Abnormal in CBF or MTT maps
		• Threshold values have not been established

MRP	• DWI is most sensitive and specific marker • CBV reduction is a generally accepted marker—should correlate with restricted diffusion	• Definite perfusion parameter has not been clearly defined • CBF reduction and MTT prolongation are sensitive indicators • MRP/DWI mismatch has been shown useful in small clinical trials

infarct core and penumbra applies thresholds to the MTT, CBF, and CBV values.[65–68] In one study, PCT was compared with DWI (infarct core) and follow-up FLAIR image abnormalities in patients with persistent occlusion (infarct penumbra). An absolute CBV of less than 2 ml per 100 g best defined infarct core and a relative MTT of greater than 145% best defined infarct penumbra.[64] In another study, comparing hypoperfused tissue on CT-CBV and CT-CBF to follow-up infarction, a relative CBV of 0.60 and a relative CBF of 0.48 best discriminated between infarcted and noninfarcted tissue.[66] In a third study, ischemic regions with greater than 66% reduction in CT-CBF ratio had a 95% positive predictive value for infarction regardless of recanalization status.[67] To date, however, there is no high-level evidence or consensus for these core and penumbra thresholds.[16,69]

Advantages

Compared with MRP, CTP has advantages of speed, lower cost, and widespread availability. CTP can be performed immediately following unenhanced CT (to exclude hemorrhage, large hypodense infarct, or mass lesion) and CTA (to evaluate for the presence of a vascular lesion). CTP parameters of CBV, CBF, and MTT may be more easily quantified than their MRP counterparts, owing in part to the linear relationship between iodinated CT contrast concentrations and CT image density. The major clinical advantage of CTP is that it can safely be used in patients who cannot undergo MR imaging. CTP, particularly when combined with CTA, provides an invaluable alternative for the estimation of both the infarct and the ischemic penumbra, and a significant improvement in the detection of infarction over NCCT alone.[70,71]

Disadvantages

One major disadvantage of CTP is that it is not as sensitive as DWI for the detection of acute ischemia. There is no universally accepted correlate for DWI, leaving the infarct core to be estimated by either one or a combination of perfusion parameters. Different postprocessing software from different manufacturers tested on the same data sets give a wide range of absolute and relative CBV, CBF, and MTT thresholds for

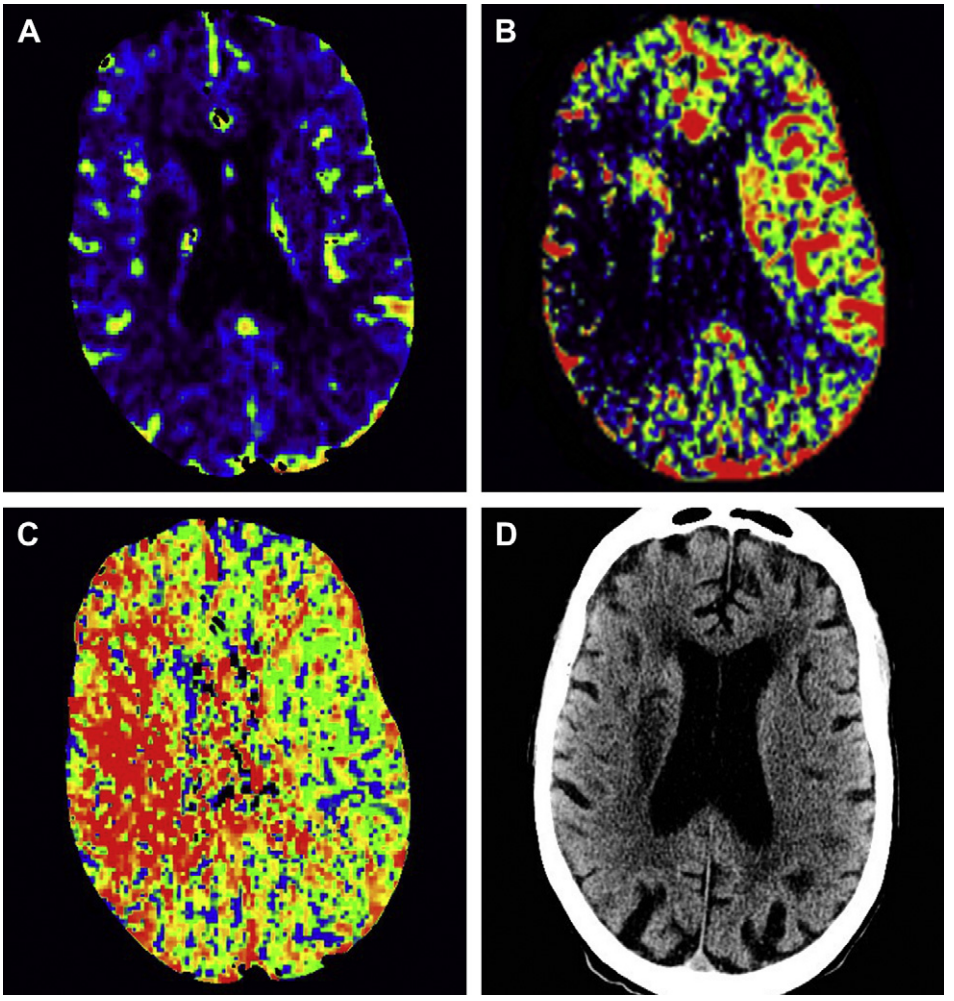

Fig. 10. Right middle cerebral artery territory infarct on CT perfusion. A 78-year-old woman with history of atrial fibrillation presenting 3 hours following left face, arm, and leg weakness, and dysarthria. CBV maps (*A*) demonstrate focal decreased cerebral blood volume in the right corona radiata. CBF maps (*B*) demonstrate a much broader region of decreased cerebral blood flow conforming to the right middle cerebral artery vascular territory. There is corresponding prolonged mean transit time on MTT maps (*C*). Intravenous rtPA was administered. Follow-up NCCT (*D*) at 1 month demonstrates the completed infarct involving mainly the corona radiata and closely approximating the original cerebral blood volume map lesion. In this case, the entire ischemic penumbra recovered.

infarct core and penumbra. This variability needs to be addressed in definitive trials, with validation of optimal postprocessing and image interpretation procedures, followed by standardization of methodology.[69] Once standardized, the technique must be confirmed by large clinical trials before the additional radiation exposure (approximately 3.35–6.7 mSv)[45] and contrast boluses are justified for routine clinical use.

The other major disadvantage of CTP is limited coverage. Although coverage varies depending on manufacturer and generation of multidetector scanner, a 16-detector scanner is able to image a 2-cm thick section per contrast bolus and a 64-detector scanner can image up to 4 cm. By way of reference, evaluation of the anterior circulation requires 8 cm of craniocaudal coverage. Several techniques have attempted to increase coverage, but have their own trade-offs. With the "shuttle-mode perfusion technique," the scanner table moves back and forth switching between 2 different cine views, albeit at a reduced temporal resolution of data acquisition.[72] Alternatively, 2 boluses can be used to acquire 2 slabs of CTP data at different levels, doubling the overall coverage.[66] Unlike the shuttle mode, this technique

requires twice the amount of contrast and twice the radiation dose. Coverage volume will continue to increase with enlarging detector arrays and improved technology. Cutting-edge scanners with 320 detector rows offer the possibility of 16-cm coverage without the decreased temporal resolution required with the shuttle-mode technique.

MR Perfusion

Technique

MRP imaging is generally performed with a bolus tracking technique, dynamic susceptibility contrast (DSC) imaging. DSC relies on the decrease in signal caused by magnetic susceptibility effects of gadolinium as it passes through the intracranial vasculature. Because blood passes through the brain parenchyma rapidly, the most commonly used sequence is a single-shot, GRE echo planar sequence capable of multiple slice acquisitions from a single TR. Typically, gadolinium is injected rapidly (5–7 mL/s) into a peripheral intravenous catheter, and then images are obtained repeatedly as the contrast agent passes through the brain. The technique takes approximately 1 to 2 minutes, and is performed so as to track the first pass of the contrast bolus through the intracranial vasculature, without recirculation effects. Approximately 60 images are obtained for each 5-mm brain slice, covering the entire brain.[22] The images obtained in the examination are converted by a computer to contrast agent concentration-versus-time curves. The CBV is proportional to the area under the curve. The CBF and MTT are typically computed with an arterial input function and deconvolution methodology. As with CTP, the echo planar imaging data are transferred to a separate workstation on which the perfusion maps are produced.

Interpretation

With MRP, the ischemic penumbra is usually defined as the region of brain tissue that is abnormal on perfusion but normal on DWI images, that is, the region of so-called diffusion-perfusion mismatch (DPM) (**Fig. 11**). The perfusion parameter that is used to calculate this mismatch, however, has not been clearly defined. Physiologic evidence indicates that CBF reduction and MTT prolongation are more sensitive indicators of ischemic, but potentially viable tissue. CBV reduction is a generally accepted marker of infarct core, and should correlate with the region of restricted diffusion. This definition is also consistent with empiric observations that the volume of a lesion seen in early CBF or MTT maps tends to overestimate the ultimate infarct volume, and is less well correlated with final infarct volume than is initial DWI or CBV lesion volume.[73–75] Usually the MTT is used for visual interpretation, because contrast-to-noise ratios are higher on these maps than in others.

The DPM concept and its ability to successfully select patients for treatment guidance beyond 3 hours has been successfully demonstrated in several clinical trials. The Desmoteplase in Acute Ischemic Stroke trial (DIAS)[74] and the Dose Escalation of Desmoteplase for Acute Ischemic Stroke trial (DEDAS)[75] used a 20% mismatch between the MTT and DWI lesions in addition to a DWI lesion volume less than one-third of the MCA territory as trial entry criteria. Patients were given intravenous desmoteplase (a thrombolytic agent derived from bat venom) or placebo between 3 and 9 hours after symptom onset. These trials demonstrated that administration of desmoteplase was associated with dose-dependent rates of higher reperfusion and better clinical outcomes compared with placebo. In the DEFUSE (Diffusion Weighted Imaging Evaluation for Understanding Stroke) study, 74 patients recruited on the basis of a negative NCCT received intravenous rtPA within 3 to 6 hours after stroke onset. Early reperfusion was associated with a significantly increased chance of a favorable clinical response in patients with at least a 20% DWI–perfusion-weighted imaging (PWI) mismatch, whereas patients without a mismatch did not benefit from early reperfusion.[76] In the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), 101 patients were recruited on the basis of a negative NCCT and received intravenous tPA or placebo within 3 to 6 hours after stroke onset; of these, 86% had a DWI-PWI mismatch. Although there was no significant difference in infarct growth between patients who received placebo and those who received intravenous tPA, there was increased reperfusion in those with a mismatch, and reperfusion was associated with less infarct growth and improved clinical outcomes.[77]

When mismatch as a target for therapy was first introduced, it was arbitrarily defined as PWI lesion 20% larger than the baseline DWI lesion volume. However, some investigators have suggested using a larger mismatch. For example, the DEFUSE investigators retrospectively determined an optimum DPM ratio of 2.6 (ie, MRP lesion 2.6 times larger than the DWI lesion) for the best chance of favorable outcome after early reperfusion.[54] More recently, Copen and colleagues[76] demonstrated that if vascular imaging demonstrates a proximal arterial occlusion, the majority of patients (80%) have a greater than 20% mismatch for up to 24 hours after stroke onset.

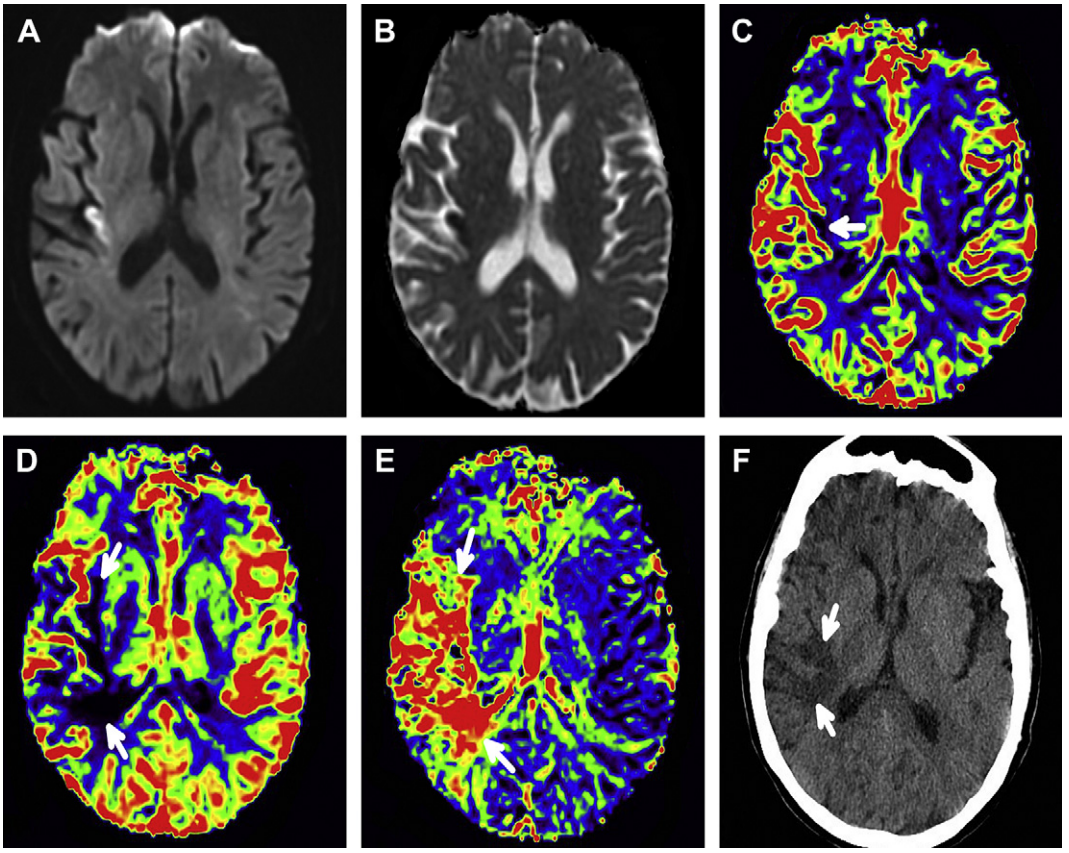

Fig. 11. Right middle cerebral artery territory infarct on MR perfusion: A 76-year-old woman with sudden-onset left-sided facial droop and weakness presented 6 hours following onset. DWI (*A*) and ADC (*B*) images revealed restricted diffusion in the right posterior insula and external capsule. There was corresponding low signal on CBV maps (*arrow* in *C*). A much larger region corresponding with the right middle cerebral artery superior division demonstrated decreased cerebral blood flow (black region indicated by *arrows* in *D*) and increased mean transit time (red and green area indicated by *arrows* in *E*). Intravenous rtPA could not be administered because the patient was outside of the therapeutic window. A follow-up CT obtained 2 days later (*F*) showed that the infarct extended into part, but not all of the ischemic penumbra.

These studies raise the possibility that imaging-based treatment protocols may appropriately select patients who may benefit from thrombolysis well beyond the initial hours of stroke symptom onset.

Advantages

The major clinical advantage of MRP is the fact that it can be easily combined with DWI, the single best imaging method for identifying infarct core, and unlike CT, it provides whole brain coverage. In addition, as already described, the use of the DPM to select patients for therapy and potentially improve patient outcomes has been validated in small clinical trials. The major technical advantages of MRP over CTP include whole brain coverage and lack of radiation. MRP also produces images with a higher contrast-to-noise ratio.

Disadvantages

The major technical disadvantage of MRP is the lack of linearity between signal intensity and contrast concentration, which makes quantification of perfusion parameters very difficult and unreliable. The major clinical disadvantage is that although widely accepted and used in practice, the diagnostic and clinical utility of MRP has not been proven in controlled, adequately powered studies. Individual centers have demonstrated that different MRP parameters are generally predictive of tissue fate and clinical outcome; however, there has been no determination of which technique is most accurate. Contributing to the lack of consensus is the variability in definitions of what represents ischemic core, penumbra, and final infarct size, and how they relate to clinical outcome on which the measures of accuracy are based.

IMAGING AND TREATMENT ALGORITHM

Based on the practical considerations and clinical trial data mentioned here, the authors have developed the following algorithm for imaging management of acute stroke patients in their Emergency Department (ED) (**Fig. 12**). On arrival and initial clinical assessment, including the NIHSS, patients are quickly transported to the ED CT scanner. Noncontrast head CT is obtained and evaluated at the scanner by the on-call radiologist to exclude hemorrhage and infarction in greater than one-third of the MCA territory or 100 cm^3 (measured by ABC/2). If neither is present and the patient has no other contraindications, intravenous rtPA can be administered by the clinical team. CTA of the head and neck vessels is then obtained, with an additional immediate delay scan from the aortic arch to the circle of Willis if there is incomplete arterial opacification. The decision of whether to give intravenous contrast is a clinical one, based in part on the patient's estimated risk of renal impairment and NIHSS score. The CTA source images and immediate postprocessed triplane MIP images are then reviewed by the radiologist at the scanner. Whether to perform CTP imaging, which requires an additional contrast bolus, is decided by the stroke neurologist, largely based on the patient's MR compatibility, clinical stability, and renal function. If the patient can undergo MR scanning, he or she is transferred from CT to a mobile MR table and brought to the MR imaging scanner. If MR imaging is not deemed appropriate and there is concern for a potentially large ischemic penumbra, CTP can be obtained.

For MR imaging, DWI is always obtained because it is the best method for determining infarct core. FLAIR is obtained if the time of stroke onset is unknown because a DWI abnormality without a FLAIR abnormality likely represents an infarction that is less than 6 hours old. If the region of restricted diffusion is large (>100 cm^3), no intervention is indicated and additional imaging is not needed. If the region of completed infarction is small (<100 cm^3), indicating that there is a potentially large territory at risk, MRP imaging should be considered. Lastly, MRA can be performed if the vessels have not already been adequately evaluated with CTA.

BEYOND IMAGING: METHODS OF TREATMENT

Neuroendovascular interventions, which include procedures such as local intra-arterial thrombolysis and the mechanical removal of thrombus, are

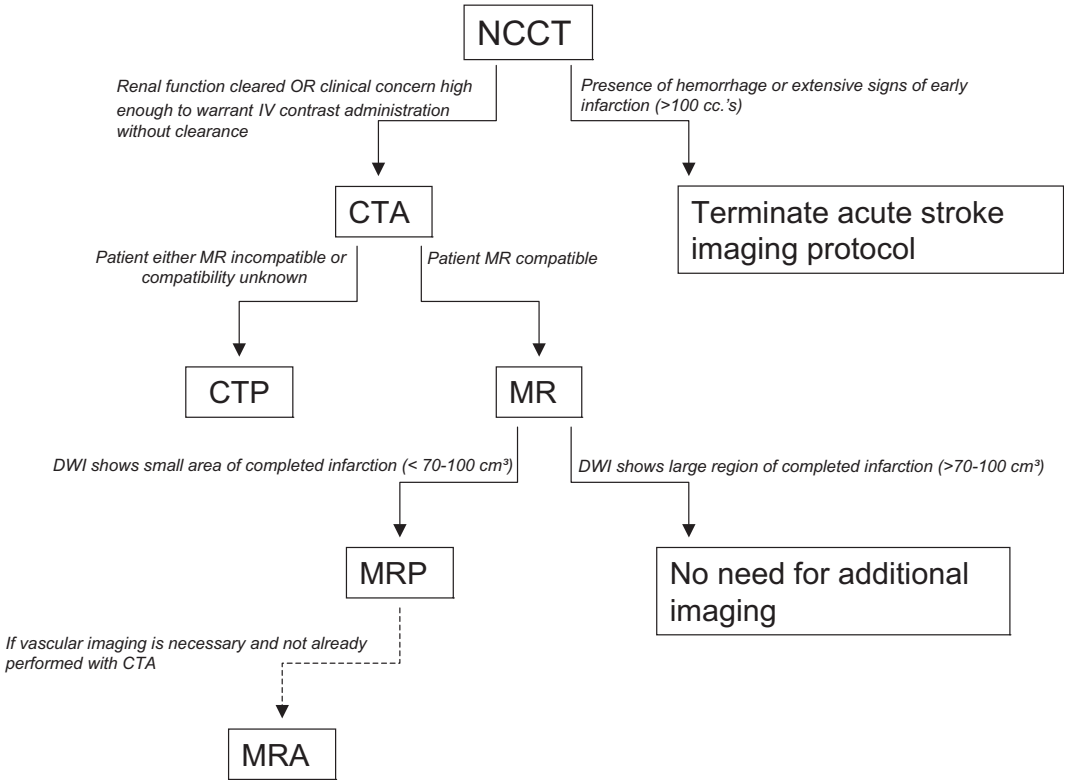

Fig. 12. Algorithm for imaging management of acute stroke patients in the authors' Emergency Department.

largely reserved for acute ischemic stroke patients who cannot safely receive (ie, present outside of the 3–4.5 hour time window), or who have failed intravenous rtPA therapy, and in whom imaging has shown a large region of potentially salvageable tissue. A complete review of these interventions is beyond the scope of this article, however, interested readers are referred to recent reviews by Janjua and Brisman[78] and Nogueira and colleagues.[79,80]

Although guidelines for the endovascular treatment of acute ischemic stroke vary largely by institution, general inclusion and exclusion criteria have been established by large clinical trials. First and foremost, the level of clinical concern prior to intervention must be high. This level is usually assessed using the NIHSS score, and several studies have used a score of at least 10 to triage patients for adjunctive endovascular treatment.[81,82] Convincing data support the safety of local intra-arterial thrombolysis if performed within 6 hours of symptom onset.[83–85] Mechanical thrombectomy is safe and effective for revascularizing occluded vessels in patients up to 8 hours after symptom onset.[81,86,87] For strokes involving the posterior circulation, the therapeutic window can be increased to 24 hours.[88–90] This unconventional time window is allowed because untreated basilar occlusion has a nearly uniform fatal outcome, and the regions served by the posterior circulation may be more resistant to reperfusion injury and hemorrhage owing to their collateral blood supply patterns.[91]

At their institution, the authors honor additional specific guidelines based on clinical data mentioned above. If a patient has a proximal vessel occlusion and an infarct core (DWI, NCCT, CT-CBV) less than 100 cm^3, then intra-arterial recanalization should be considered. If a patient is not a candidate for recanalization and has a proximal or distal occlusion with a core penumbra (usually MTT or other transit time measures) mismatch, then the patient should be closely monitored in the intensive care unit with special attention to keeping his or her blood pressure relatively high to preserve cerebral perfusion pressure to the ischemic tissue at risk of infarction. If the core and penumbra volumes are matched, the infarction is not at risk of extending and aggressive therapy is not required.

SUMMARY

Nearly 1.5 decades after the introduction of systemic thrombolysis for the treatment of acute ischemic stroke, we are now entering an era of newer imaging and image-guided interventions that can both extend the time window for potential treatment and provide a targeted, patient-specific therapeutic approach. Both CT and MR imaging provide promising tools for evaluating the brain parenchyma, with distinct advantages that can be maximized for the individual patient's needs. Although further work and investigation are required to standardize practice guidelines and improve patient access, advanced imaging techniques and endovascular treatments will hopefully offer alternatives to patients who are otherwise without therapeutic options.

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