AHA Scientific Statement

Recommendations for Imaging of Acute Ischemic Stroke

A Scientific Statement From the American Heart Association

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Stroke is a common and serious disorder, with an incidence of ≈795 000 each year in the United States alone. Worldwide, stroke is a leading cause of death and disability. Recombinant tissue plasminogen activator (rtPA) was approved a decade ago for the treatment of acute ischemic stroke. The guidelines for its use include stroke onset within 3 hours of intravenous drug administration, preceded by a computed tomographic (CT) scan to exclude the presence of hemorrhage, which is a contraindication to the use of the drug. Although randomized, controlled studies in Europe and North America demonstrated the efficacy of this treatment, it also was associated with an incidence of intracranial hemorrhage of 6.4%,[1,2] which was shown on subsequent studies to be even greater if there was not strict adherence to the administration protocol.[3] The goal of these controlled studies was to evaluate patient outcome. There was no attempt to determine the site, or even the actual presence, of a vascular occlusion, the degree of tissue injury, or the amount of tissue at risk for further injury that might be salvageable.

More than a decade later, progress for treating acute ischemic stroke has been slow,[4,5] yet the goals for treating this common disease have expanded. First, there is the need to extend the therapeutic window from 3 to ≥6 hours. Even with the rapid communication and transportation in our societies today, very few patients present for treatment within 3 hours.[6] Second, there is the desire to improve the efficacy of treatment. It had been shown even before the randomized, controlled studies that intravenous rtPA works better in small peripheral vessels than in the large vessels at the skull base.[7] Third, there is a need to decrease the complication rate, especially if patients are to be treated later in the course of the ischemic process.

How are these goals to be achieved? First, new therapies are being developed. The efficacy of new intravenously administered thrombolytic drugs may be better than rtPA, while associated with fewer complications.[8] The intra-arterial administration of a thrombolytic agent is not a new technique,[9] but no agent has yet been approved for intra-arterial delivery to treat acute stroke. A number of devices have either been approved[10] or are under evaluation for the performance of intra-arterial mechanical thrombectomy. The hope is that these devices will partially or totally remove an occluding thrombus without requiring any, or as much, of the drugs associated with hemorrhage. Such an approach (starting with an intra-arterial therapy instead of the administration of an intravenous drug) requires that vascular imaging be performed during the initial imaging assessment of the patient.

Second, the patient may be triaged for appropriate management with improved imaging techniques beyond a simple CT scan.[4,5] To extend the therapeutic window, improve efficacy, and limit complications, imaging should address 4 essential issues: (1) the presence of hemorrhage; (2) the presence of an intravascular thrombus that can be treated with thrombolysis or thrombectomy; (3) the presence and size of a core of irreversibly infarcted tissue; and (4) the presence of

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hypoperfused tissue at risk for subsequent infarction unless adequate perfusion is restored.[11–13] There are now a myriad of imaging tests for evaluation of these 4 issues, with the number of new and improved magnetic resonance (MR) and CT techniques virtually exploding during the past decade. MR diffusion-weighted imaging (DWI) is the most sensitive and specific technique available for demonstrating acute infarction within minutes after its occurrence,[14] and this can be combined with MR perfusion (MRP) to differentiate viable from probably nonviable hypoperfused tissue.[15–17] In the same examination, MR angiography (MRA) can demonstrate the vascular occlusion, whereas a gradient-recalled echo (GRE) sequence excludes intracerebral hemorrhage (ICH).[18] The fluid-attenuated inversion recovery (FLAIR) sequence is now routine and is the best method for showing abnormal accumulations of fluid. Such a combination of MR sequences can be performed in 10 minutes.[19] With multidetector scanners, nonenhanced CT (NECT) scanning of the head can be performed in a matter of seconds to evaluate hemorrhage and other insults to the brain; CT angiography (CTA) from the aorta to the top of the head can be performed in less than a minute; and the source images from that CTA (CTA-SI) can provide a qualitative cerebral blood volume (CBV) map that detects the core of infarction and improves the demonstration of the tissue at risk for infarction compared with NECT.[20–22] Quantitative (dynamic) CT perfusion (CTP) can be focused on the tissue at risk during the same imaging session to differentiate infarcted from oligemic but probably viable tissue.[23] Imaging at a single point in time presents only a portion of the desired information, with the evolution of tissue perfusion and viability the ultimate goal. The decision to treat acute stroke with a variety of chemical agents and devices requires that essential information be obtained rapidly, however; the treating physician does not have the luxury of acquiring multiple data points over time. Thus, the newest imaging methodologies should be viewed as excellent methods for patient triage.

Which of these many techniques should be used by the medical team, made up of imaging specialists and clinicians? There are many factors to consider, such as the differential diagnosis, availability and reliability of the technique, time for performance, expertise required for performance and interpretation, cost, and both patient monitoring and comfort. A recent symposium attended by imagers and clinicians from many subspecialties within the neurosciences produced by consensus a roadmap for the use of a variety of imaging techniques.[24] The goals of this ongoing research group will be to determine the accuracy of the various modalities, their ability to triage a patient for therapy, and their role in assessing patient prognosis and outcome; however, that group did not undertake an in-depth review of the literature regarding their current status. Thus, it is appropriate that a review of the literature be undertaken to determine the current state of various imaging techniques and procedures in terms of what they offer relative to what we need to know to provide proper medical management. This imaging analysis can be divided into 3 components: Imaging of the cerebral parenchyma, imaging of the blood vessels, and perfusion imaging to assess tissue viability. The review has been confined to the English literature and includes all relevant articles but focuses on the literature from 2000 to 2006, with some more recent. The quality of each article has been assessed for its level of evidence (LOE), per Table 1. From this analysis, guidelines and recommendations have been proposed, with the class (strength) of each recommendation based on the LOEs (Table 2). The definitions for the LOEs and classes of recommendations conform to the American Heart Association's practice guidelines classification scheme. When the LOEs are weak and a firm guideline or recommendation cannot be established, trends are discussed and suggestions made for further studies.

Table 1. Levels of Evidence

A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized trial or nonrandomized studies
C	Only consensus opinion of experts, case studies, or standard-of-care

Imaging the Cerebral Parenchyma

CT and MR imaging (MRI) are used for imaging of the density and intensity, respectively, of the cerebral parenchyma and its anatomic structure. The 3 roles of these imaging modalities in assessing the status of brain tissue in the acute stroke patient are the same: the exclusion of hemorrhage, the detection of the ischemic tissue, and the exclusion of conditions that mimic acute cerebral ischemia. The ability of each modality to determine the amount of salvageable versus nonviable tissue depends on the perfusion techniques that each can perform, which will be discussed below.

Evaluation of the literature must be done with the recognition that the ability of each modality to accomplish these 3 goals has improved progressively over the past decade, which makes comparative evaluation more difficult. The perfection of multidetector technology has enabled a CT scan of the head to be obtained with submillimeter slice thickness in a few seconds and with superior tissue differentiation (contrast resolution) to the past. The speed of MR image acquisition and reconstruction has decreased markedly, the quality of the images has improved, and the diversity of the pulsing sequences has increased significantly. The latter is exemplified by the development of DWI to detect ischemic tissue within minutes of its occurrence, the perfection of the FLAIR sequence that permits the detection of subtle intraparenchymal and subarachnoid fluid collections far better than other sequences, and the common use of gradient-echo (magnetic

Table 2. Classification of Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that a procedure or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful

susceptibility) imaging to detect acute parenchymal hemorrhage and thrombus formation.

Exclusion of Hemorrhage

Intracerebral Hemorrhage

It is usually assumed that CT is the gold standard for the detection of ICH. In fact, there are no level A studies, which use a true gold standard such as immediate surgery or autopsy, to determine the sensitivity and specificity of CT in detecting acute ICH. Most imagers and clinicians have long assumed the high accuracy of CT in demonstrating parenchymal blood on the basis of a few level C studies with early CT scanners[25,26] and practical experience. Two prospective and randomized level A studies used CT in the evaluation of intravenous tissue plasminogen activator (tPA) for the treatment of cerebral ischemia within 3 hours of onset, in which the exclusion of intracranial hemorrhage was mandatory for the administration of the thrombolytic agent.[1,2] However, the accuracy of CT was not being evaluated, and the participants in these studies assumed the high sensitivity of CT for this detection.

The appearance of ICH on MRI is dependent on both the age of the blood and the pulsing sequences used.[18,27–33] Magnetic susceptibility imaging is based on the ability of a T2*-weighted MR sequence to detect very small amounts of deoxyhemoglobin, in addition to other compounds such as those that contain iron or calcium. During the past few years, numerous authors have described anecdotal series in which these gradient-echo techniques have demonstrated cerebral hemorrhage.[34] In a 2004 study, gradient-echo MRI was performed followed by NECT in 200 patients presenting with stroke symptoms of ≤6 hours. Although the gold standard was the consensus of 4 blinded readers, they found that MRI and CT were equivalent in detecting acute hemorrhage (96% concordance). In 4 patients, MRI demonstrated hemorrhagic transformation of areas of ischemia that the CT did not detect. In another 49 patients, deposits of chronic hemorrhage (microbleeds) were visualized on MRI but not on CT. The conclusion was that the MR GRE sequence appeared to be at least as accurate as CT for the detection of acute ICH.[18] Does the presence of tiny amounts of hemorrhage seen on MR but not CT contraindicate the use of a thrombolytic agent? Recent evidence (level B) suggests that although the presence of old microbleeds may predict recurrent disabling and fatal strokes, there was no statistically significant increase in the risk of symptomatic ICH when patients with a small number of microhemorrhages (<5) on MR were treated with intravenous thrombolysis.[35] The risk in patients with multiple microbleeds (>5) is underdetermined.

Subarachnoid Hemorrhage

Although the clinical presentation of subarachnoid hemorrhage (SAH) is sufficiently different from the presentations of either acute ICH or cerebral ischemia in most cases, it is important to exclude the presence of SAH if the administration of a thrombolytic agent is considered, as well as to determine the cause of the SAH once detected (eg, aneurysmal rupture). Studies comparing CT and lumbar puncture are numerous and have demonstrated the high sensitivity of CT in detecting SAH.[36–39] In fact, it is this proven ability of CT to detect small amounts of SAH that has led to the assumption that CT has a high sensitivity for the detection of any acute intracranial hemorrhage.

FLAIR, an MRI sequence, nulls the signal from cerebrospinal fluid, which enables the detection of tiny amounts of hyperintense fluid, be it blood or an inflammatory exudate, within the subarachnoid spaces. Level C studies have demonstrated the ability of FLAIR to detect SAH, proven with subsequent CT and lumbar puncture[40]; however, prospective randomized studies have not been performed. In addition, cerebrospinal fluid turbulence within prepontine and other basilar cisterns produces increased signal, which simulates subarachnoid blood/exudate as a false-positive sign on the FLAIR sequence.

Detection of Cerebral Ischemia and Exclusion of Mimics

The dual roles of detecting the ischemic tissue to ensure the diagnosis while excluding mimics such as tumor or subdural hematoma are heavily dependent on the contrast resolution of the imaging system. Although MRI greatly exceeds NECT in such resolution, NECT traditionally has been used to assess the acute stroke patient because of its speed and availability.

Findings on NECT

A significant early CT sign of cerebral ischemia within the first few hours after symptom onset is loss of gray-white differentiation, because there is an increase in the relative water concentration within the ischemic tissues.[39–43] This sign includes loss of distinction among the nuclei of the basal ganglia and a blending of the densities of the cortex and underlying white matter in the insula and over the convexities. The subsequent swelling of the gyri produces sulcal effacement, which may lead to ventricular compression. The sooner these signs become evident, the more profound is the degree of ischemia. However, the ability of observers to detect these signs on NECT is quite variable, depending on the size of the infarct, the time between symptom onset and imaging, and the methodology of the trial itself; the detection rate appears to be ≤67% in cases imaged within 3 hours.[44–48] In a post hoc analysis of the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study, Patel et al[49] found 31% sensitivity for these early infarct signs. The rate of detection increases to 82% at 6 hours, which is outside the therapeutic window for intravenous rtPA.[50] Such detection may increase with the use of scoring systems such as the Alberta Stroke Program Early CT Score (ASPECTS),[51,52] as well as with the use of better CT windowing and leveling to differentiate the normal and abnormal tissues.[53]

The significance of these early CT signs has been debated. In the European Cooperative Acute Stroke Studies (ECASS), patients with large infarcts with early swelling had an increased incidence of hemorrhage and poor outcome with the use of rtPA, and so it was considered essential to detect them.[43,50] Conversely, Patel et al[49] demonstrated that in the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study, such extensive early CT signs of infarction were associated with stroke severity but not with adverse outcome after rtPA treatment. They concluded that such early CT signs should not be used to exclude patients from receiving thrombolytic treatment within 3 hours.[49] However,

Schellinger et al[54] have argued that Patel et al[49] did not evaluate whether the outcome might have been better if rtPA had not been given to those with such extensive early signs and that such extensive signs are typically found in patients presenting in the 3- to 6-hour time window. Thus, the NECT criteria of Schellinger et al for withholding rtPA in the 0- to 3-hour time window are hemorrhage or definite signs of ischemia that exceeds one third of the middle cerebral artery (MCA) territory.[54]

Another significant CT sign is that of increased density within the occluded vessel, which represents the thrombus. When this is the MCA, it is called the hyperdense MCA sign, and it is seen in one third to one half of all cases of angiographically proven thrombosis.[55,56] Hence, it is an appropriate indicator of thrombus when present, but its absence does not exclude thrombus. Attempts have been made to determine the composition of a thrombus with CT, which might aid in the decision to use intra-arterial rtPA or thrombectomy if a hard white clot is present.[57] Unfortunately, the apparent density of a small but occluding thrombus can be altered by partial volume averaging with adjacent calcium, cerebrospinal fluid, fatty atheromatous material, and other tissues, and thus, determination of its composition is not accurate.

Findings on MRI

The ability of MRI to detect cerebral ischemia is dependent on the sequence used, and these sequences have evolved over time. The most important of these is DWI, based on the demonstration of restricted diffusion as extracellular water moves into the intracellular environment during ischemia, accompanied by swelling of cells and narrowing of the extracellular spaces. The isotropic DWI map makes abnormal areas of ischemia readily visible. However, because the diffusion sequence is T2-based, shine-through of high T2 abnormalities, such as vasogenic edema, may be misinterpreted. Thus, correlation with the apparent diffusion coefficient map, which demonstrates restricted diffusion as low intensity, greatly increases the specificity of the technique. Alternatively, the calculated isotropic diffusion value of each pixel on the DWI map may be divided by the T2 value of each pixel to derive an exponential image that eliminates the T2 shine-through, again greatly increasing specificity for true restricted diffusion. A series of level A and B studies have demonstrated convincingly that DWI is significantly better than FLAIR and T2-weighted MRI, and much better than CT, for detecting an ischemic focus within 6 hours of ictus.[58–61] Gonzalez et al[62] demonstrated the very high sensitivity and specificity of DWI for the diagnosis of acute ischemia using the final clinical and imaging diagnoses as gold standards. Barber et al[63] demonstrated 100% sensitivity to ischemia with DWI versus 75% with CT within 6 hours. Because there was a time delay between the CT and MR studies in that project, Fiebach et al[14] undertook a randomized crossover comparison of DWI and CT within 6 hours of symptom onset, which demonstrated a sensitivity/specificity for DWI of 91%/95% versus 61%/65% for CT. Thus, DWI has emerged as the most sensitive and specific imaging technique for acute ischemia, far beyond NECT or any of the other MRI sequences. In addition, additional MR sequences provide the ability to detect other types of lesions that may mimic acute ischemic stroke.

There are a few anecdotal papers describing negative DWI studies when cerebral perfusion is decreased enough to produce infarction,[64,65] as well as the reversal, partial or complete, of DWI abnormalities with restoration of perfusion.[66] Thus, DWI is not a simple indicator of irreversible infarction but a complex variable that requires more study. In addition, other conditions can produce restricted diffusion, such as infection (eg, abscesses, aggressive viral infections) and other inflammatory conditions (eg, aggressive demyelination), and certain tumors with either little cytoplasm (eg, lymphoma, meningioma) or with a complex internal architecture (epidermoid, some metastases).

The MCA clot sign can be seen on MRI and CT. A direct comparison of CT and MRI in patients with occlusion of the proximal MCA found that 54% of patients demonstrated this sign on CT, whereas 82% of the same patients had a clot demonstrated on MRI with a GRE sequence.[56] Sheikh et al[67] have recently presented their data that indicate that CTA is better than GRE for a proximal arterial thrombus, but GRE is superior to CTA for a more distal clot. Hyperintensity of an intravascular thrombus is also seen on the FLAIR sequence. One group has recently found that the sensitivity for detection of a thrombus on GRE is actually less than that for FLAIR but exceeds that of NECT.[68] Other, more subtle signs include the loss of a flow void within a fast-flowing large artery at the skull base on T2-weighted studies, whereas more peripheral cortical vessels demonstrate contrast enhancement due to stasis.[69] As with CT, thrombus characterization with MR has proved difficult because of the small size of the clot and the relative values of tissue-intensity measurements with MR.[70]

Findings on CTA-SI

The source images of the brain during CTA acquisition, which reflect blood volume, make a focus of hypoperfusion much more detectable than does the NECT. Lev et al[20] demonstrated the very close correlation between the size of the infarct on CTA-SI and that which was demonstrated on follow-up CT studies. This same study also demonstrated that those patients with large infarcts (>100 mL, equivalent to more than one third of the MCA distribution) had significantly poorer outcomes after intra-arterial recanalization than did those with small infarcts as demonstrated with CTA-SI. CTA/CTA-SI was compared with NECT plus history in 40 patients in a blinded study that demonstrated marked improvement in localization of both the infarct and the occluded vessel(s) with the use of CTA/CTA-SI.[71] Direct comparisons of CTA-SI and DWI have demonstrated the extremely close sensitivity of the 2 techniques in detecting ischemic regions, with DWI better at demonstrating smaller infarcts and those in the brain stem and posterior fossa.[72,73] The overall LOE for CTA-SI is a strong B. Analogous to the improved detection with CTA-SI, dynamic quantitative CTP has recently been shown in level B studies (addressed more fully elsewhere herein) to dramatically increase the sensitivity for detection of an ischemic focus from 46% to 58% by NECT to 79% to 90% by CTP.[74]

Study Acquisition Time

The acquisition time for NECT with a multidetector scanner is 1 to 2 minutes. The addition of CTA/CTA-SI and dynamic CTP to NECT recently has been shown to increase the time of the total examination from 2 to 10 minutes.[74] One of the major arguments against the routine use of MRI for the evaluation of the acute stroke patient is the time required to perform the numerous pulsing sequences. Schellinger et al[19] have been leaders in demonstrating that a diagnostic examination that consists of DWI, FLAIR, GRE, MRP, and intracranial MRA can be performed in 10 minutes, thus making it competitive with CT, especially if CTA and CTA-SI are added to equal the diagnostic yield of the MR examination. To date, there have been no randomized series to compare these techniques and their time requirements directly. Although the total time for imaging must include such things as transferring the patient to the scan table, positioning the patient, data entry, and the placement of an intravenous line, both of the studies noted above, 1 of which used CT and another MR, took into account all of these variables in acute stroke patients who came to the scanner with an intravenous line in place. The major problem with MR as an imaging technique to triage the acute stroke patient to appropriate therapy is access to the scanner, which is really a function of the ability of an institution to provide this resource on an emergency basis. If MRI/MRA is proven to be indispensable to the diagnosis and triage of the acute stroke patient, and if reliable therapies are developed, adequate MR resources will be demanded, and access will improve.

Summary

1. It is important to remember that the US Food and Drug Administration did not require an NECT scan, only that ICH be excluded within 45 minutes for performance and interpretation of any study before the administration of intravenous tPA. The use of MRI and contrast-enhanced CT studies (CTA, CTA-SI) is therefore justifiable, but their acquisition cannot unduly delay the administration of intravenous tPA within the 3-hour time window (LOE: A).
2. MRI appears to be at least equal in efficacy to CT for detection of ICH in the hyperacute stroke patient, and both appear to have very high sensitivity and specificity (LOE: B). MRI is superior to CT for demonstration of subacute and chronic hemorrhage and hemorrhagic transformation of an acute ischemic stroke (LOE: B).
3. The gradient-echo MR sequence can detect microhemorrhage, both old and new, better than CT, indicating the presence of amyloid angiopathy, hypertension, small vascular malformations, and other vascular diseases (LOE: strong B). The presence of a small number of these microhemorrhages (<5) does not contraindicate intravenous thrombolysis (LOE: B).
4. DWI is far superior to NECT and other routine MRI sequences in the detection of acute ischemia, with very high sensitivity and specificity (LOE: A).
5. CTA-SI appears to be as good as DWI at detecting acute ischemia, with the exception of small foci and those in the posterior fossa (LOE: B).
6. NECT is excellent at detecting SAH (LOE: A). Although the FLAIR sequence is also very effective at such detection (LOE: C), the lack of randomized trials makes direct comparison impossible at this time.
7. Both GRE and FLAIR exceed the sensitivity of NECT for the detection of thrombus within the vasculature in the acute stroke patient (LOE: B).
8. Within the 3-hour window from the onset of symptoms, the use of intravenous tPA is the US Food and Drug Administration–approved therapy. NECT has been used as the imaging modality to exclude hemorrhage because it is usually more accessible than MRI. However, the ideal would be to use the more sensitive and specific imaging modality, MRI, to detect hemorrhage and ischemic tissue, if this examination does not unduly delay the administration of intravenous tPA. Similarly, it would be ideal to obtain vascular imaging studies such as CTA and MRA if they do not unduly delay the administration of intravenous tPA and if an endovascular team is available to potentially use the data to triage the patient to intra-arterial therapies (see "Imaging the Cerebral Vasculature"; LOE: B).

Recommendations

1. For a patient within a 3-hour time period from onset of symptoms, either NECT or MRI is recommended before intravenous tPA administration to exclude ICH (absolute contraindication) and to determine whether CT hypodensity or MRI hyperintensity of ischemia is present. Frank hypointensity on CT, particularly if it involves more than one third of an MCA territory, is a strong contraindication to treatment. Early signs of infarct on CT, regardless of their extent, are not a contraindication to treatment. (Class I, LOE: A).
2. For a patient within 3 hours of onset of symptoms, there is a suboptimal detection rate of ischemic changes with NECT alone, and a more definitive diagnosis will be obtained with MR-DWI or CTA-SI as detailed below if this does not unduly delay the administration of intravenous tPA:
   a. MR-DWI surpasses NECT and other MR sequences for the detection of acute ischemia. The MR sequences accompanying DWI are more effective than CT for excluding some mimics of acute cerebral ischemia, and thus, MRI can be used if it does not unduly delay the timely administration of intravenous tPA. (Class IIa, LOE: B).
   b. CTA-SI exceeds NECT and may approach DWI for the detection of large ischemic regions, and although it is less effective for demonstrating small lesions or those in the posterior fossa, it is reasonable to use (Class IIa, LOE: B).
   c. A vascular study is probably indicated during the initial imaging evaluation of the acute stroke patient, even if within 3 hours from ictus, to further determine the diagnosis of acute stroke, if such a study does not unduly delay the administration of intravenous tPA and if an endovascular team is available (see "Imaging the Cerebral Vasculature"; Class IIa, LOE: B).
3. For patients beyond 3 hours from onset of symptoms, either MR-DWI or CTA-SI should be performed along with vascular imaging and perfusion studies, particularly if mechanical thrombectomy or intra-arterial thrombolytic therapy is contemplated (Class I, LOE: A).
4. Although a gradient-echo MR sequence can be useful during initial evaluation, the presence of MRI-detected

cerebral microbleeds, in the absence of unenhanced CT-detected hemorrhage, is not a contraindication to intravenous tPA within 3 hours of stroke onset in patients with a small number of microbleeds (Class IIa, LOE: B); the risk in patients with multiple microbleeds (>5) is uncertain (Class IIb, LOE: B).

5. a. CT is recommended for the detection of SAH (Class I, LOE: A).
   b. However, if MR is being used to image the patient, the FLAIR sequence can also be used, although there may be some artifacts at the skull base (Class IIa, LOE: B).
6. The MR GRE and FLAIR sequences can be useful instead of CT if intravascular thrombus detection is desired without the use of vascular imaging techniques (Class IIa, LOE: B).

Imaging the Cerebral Vasculature

An important aspect of the workup of patients with stroke, transient ischemic attack (TIA), or suspected cerebrovascular disease is the imaging of the extracranial and intracranial vasculature. The majority of strokes and TIAs are due to disease in ≥1 of these vessels. For the acute stroke patient, vascular imaging greatly improves the localization of the site of vascular occlusion.[71] Given that intravenous thrombolysis appears more efficacious for distal than for proximal thrombus[7] and that intra-arterial thrombolysis and mechanical thrombectomy may be more efficacious for treatment of a proximal large-vessel occlusion than intravenous thrombolysis, the detection of the site of the arterial disease may be crucial to determining the type of acute therapy to institute. It is also essential to establish as soon as possible the mechanism of ischemia to prevent subsequent episodes. For chronic cerebrovascular disease, determination of the vessels that are diseased is paramount for patient management, which may require carotid endarterectomy (CEA) or angioplasty and stenting. These same procedures are occasionally performed in the acute setting of cerebral ischemia. A variety of imaging modalities are widely available, relatively safe and reliable, and each technique has particular strengths and weaknesses. Given all of these roles for vascular imaging, it is appropriate to consider them all, even if some are used more frequently for chronic cerebrovascular disease. The technical aspects and clinical evidence for each modality will be reviewed, with the understanding that imagers and clinicians will use their clinical judgment in each case to provide the best possible care.

Carotid Ultrasound

Introduction and Methods

Ultrasound techniques have been described in numerous texts. Pulse-wave Doppler ultrasound can identify significant luminal narrowing based on increased velocity of blood flow across a stenotic lesion. High-resolution B-mode ultrasound scanning uses linear-array transducers (7 to 12 MHz) to display morphological features of the arterial wall. Duplex sonography combines integrated pulse-wave Doppler spectrum analysis and B-mode sonography.[75] The B-mode image offers information about morphology in addition to serving as a template for accurate pulse-wave Doppler velocity measurement.[76] Color Doppler flow imaging based on the direction of flow superimposes color-coded blood flow patterns over the B-mode template. Power Doppler imaging color-codes blood flow according to the amplitude of the Doppler signal.[77,78] These latter modalities afford greater sensitivity to blood flow detection, which allows improved detection of near-occlusive stenoses, tortuosity, and other morphological abnormalities in the arterial wall.[79,80]

Table 3. Representative Criteria for the Classification of ICA Stenosis by Doppler Velocity Criteria

Velocity Criteria, cm/s	ICA Stenosis, %
PSV 110	0–29
PSV 111–130	30–49
PSV >130, EDV 100	50–69
PSV >130, EDV >100	70–99

EDV indicates end-diastolic velocity.

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Quantification of Carotid Stenosis

Catheter-based cerebral angiography (digital subtraction angiography [DSA]) is the standard against which all noninvasive assessments of carotid luminal narrowing are commonly compared. Although several methodologies have been proposed for the angiographic quantification of stenosis, the Committee on Standards for Noninvasive Vascular Testing of the Joint Council of the Vascular Societies has recommended that percent diameter reduction should be determined relative to the distal uninvolved internal carotid artery (ICA).[81] Doppler measures that have been correlated with angiographic stenosis include ICA peak systolic velocity (PSV) and end-diastolic velocity, as well as ratios of ICA PSV and common carotid artery PSV.[82]

Using receiver operator characteristic curves to compare sensitivity, specificity, positive predictive value, and negative predictive value for criteria to define degrees of stenosis relevant to clinical management, Faught et al[83] concluded that the combination of a PSV >130 cm/s and an end-diastolic velocity >100 cm/s defined a stenosis of 70% to 99% (Table 3). Using a similar approach, Moneta et al[84] concluded that an ICA PSV/common carotid artery PSV ratio >4.0 provided optimal accuracy for the diagnosis of a stenosis of 70% to 99%. A third set of criteria for the same degree of stenosis were proposed by Carpenter et al[85] that indicated that a combination of PSV >210 cm/s, end-diastolic velocity >70 cm/s, ICA PSV/common carotid artery PSV ratio >3.0, and ICA end-diastolic velocity/common carotid artery end-diastolic velocity ratio >3.3 was most accurate.

Recent publications demonstrate that Doppler test results and diagnostic criteria are influenced by several factors, such as the equipment, the specific laboratory, and the technologist performing the test.[86–88] In addition, factors such as contralateral occlusive disease have been associated with increased carotid volume flow that results in an overestimation of the severity of stenosis.[89,90] For these reasons, it is recommended that each laboratory validate its own Doppler criteria for clinically relevant stenosis.[91,92] One such methodology is to have the vascular laboratory undergo a certification process by an independent auditing organization such as the Intersocietal Commission for Accreditation of Vascular Laboratories Essentials and Standards for Accreditation in Noninvasive Vascular Testing. Studies comparing the accuracy of duplex

ultrasound examinations have noted consistently superior results from accredited versus nonaccredited laboratories.[93]

Ultrasound Assessment of Arterial Wall Morphology

Certain atherosclerotic patterns may be associated with a higher occurrence rate of cerebrovascular thromboembolic events. Histological analyses of atherosclerotic plaques have demonstrated that they originate from fatty streaks (type I) and progress through organized plaques (type IV) to complicated plaques (type VI).[94,95] Regional compositional and architectural changes within the plaque in the form of hemorrhage, lipid core expansion, lipid core proximity to flow lumen, and fibrous cap thinning may predispose to rupture and atheroembolic neurological complications.[94–97] Asymptomatic patients harboring carotid plaques with such features may be at increased risk for developing thromboembolic strokes or TIAs.[98–104] Reilly et al[105] first noted that echo patterns in B-mode images of carotid plaques could be related to tissue composition. They qualitatively defined plaque echogenicity as the degree of acoustic brightness. Goes and colleagues[106] subsequently proposed that echogenicity of plaques increased when fibrous tissue or calcium content increased. Gray-Weale et al[107] reported that predominantly hypoechoic plaques were associated with neurological symptoms. Using digital image processing to objectively measure pixel intensity (brightness) of B-mode ultrasound images, el-Barghouty et al[108] quantified the grayscale intensity of the entire plaque (grayscale median). Low grayscale median values may be associated with a higher incidence of neurological symptoms.[108–111] Digital image segmentation protocols have been proposed to accurately detect regional variations in the composition and architecture of plaques.[112] Further development of such image-analysis techniques may allow identification of tissue signatures of unstable carotid plaques with a high risk for producing ischemic events.

Accuracy of Carotid Ultrasound and CEA

There is continuing debate about the optimal imaging technique for determining the severity of carotid artery stenosis. Imaging modalities such as MRA and CTA are being used with increasing frequency to determine the degree of carotid artery stenosis. These techniques are discussed in more detail below. One study found high concordance rates among CTA, contrast-enhanced MRA (CE-MRA), and ultrasound for patients with asymptomatic carotid stenosis.[113] Another study comparing ultrasound with DSA for severe carotid artery stenosis found a sensitivity of 87.5% and a specificity of 76%.[114] When ultrasound is compared with DSA, the sensitivity for detecting surgical lesions has been as low as 65%, with specificities of 95%.[115] Other studies report sensitivities of 83% to 86% and specificities of 87% to 99% for detecting lesions with >70% stenosis.[116,117] One meta-analysis found that in most reports, all of the ultrasound studies had sensitivities of >80% and specificities of >90%.[118] Other studies comparing ultrasound and MRA to DSA for evaluation of patients for possible CEA found that ultrasound alone would have misassigned 28% of patients to the surgical group, whereas ultrasound combined with CE-MRA reduced the misassignment rate to 17%.[119,120] However, even a misclassification rate of only 15% means that almost 1 of every 6 patients evaluated may undergo an unneeded operation or may not have a needed surgery.

Table 4. Accuracy of Transcranial Doppler for Various Types of Cerebrovascular Disease

Indication	Sensitivity, %	Specificity, %	Comparator
Intracranial stenotic/ occlusive disease			
Anterior circulation	70–90	90–95	DSA
Posterior circulation	50–80	80–96	DSA
Vasospasm after SAH			
MCA	39–94	70–100	DSA
ACA	13–71	65–100	DSA
Posterior circulation	44–100	42–88	DSA

ACA indicates anterior cerebral artery.

Adapted from Nederkoorn et al,[114] with permission from Lippincott Williams & Wilkins. Copyright 2002, American Heart Association.

In summary, although carotid ultrasound/Doppler imaging is a safe and inexpensive technique, its sensitivity and specificity appear less than that of other modalities (overall LOE: A). In addition, carotid ultrasound only images a small region of the carotid and vertebral arteries in the neck. Although level A evidence indicates that it remains useful as a screening tool, level B studies indicate that carotid ultrasound should not be used as the sole methodology for the definitive diagnosis of carotid or vertebral artery disease (Class I recommendation; see below).

Transcranial Doppler

Transcranial Doppler (TCD) uses energy of 2 to 4 MHz to insonate cerebral vessels, typically through several bony windows in the skull. This technique can detect intracranial flow velocities, the direction of flow, vessel occlusion, the presence of emboli, and vascular reactivity. The arteries best evaluated are those at the base of the brain (MCA, anterior cerebral artery, carotid siphon, vertebral artery, and basilar artery) and the ophthalmic artery. The primary applications of TCD are to detect and quantify intracranial vessel stenosis, occlusion, collateral flow, embolic events, and cerebral vasospasm (particularly after SAH).[121,122] TCD is also useful for monitoring patients with sickle cell disease who might benefit from transfusion therapy.[123,124]

For the detection of intracranial stenoses in the anterior circulation, the sensitivity and specificity of TCD range from 70% to 90% and from 90% to 95%, respectively.[125–129] These numbers are slightly reduced when vessels in the posterior circulation are studied (Table 4). In these studies, cerebral angiography was generally used as the comparator. TCD was equally effective for the detection of MCA occlusion (Table 5). The ability of TCD to detect occlusion of the ICA, vertebral artery, or basilar artery was somewhat less, with sensitivities in the 55% to 80% range and specificities up to 95%.[125,130,131] These results can be improved with the use of contrast material such as saline with bubbles.[132–134] A number of underlying conditions, such as carotid stenosis, prosthetic heart valves, atrial fibrillation, patent foramen ovale, plaque in the aortic arch, and cardiopulmonary bypass, have been associated with the occurrence of microembolic signals in the cerebral circulation. TCD is capable of detecting microem-

Table 5. Sensitivity and Specificity of Contrast-Enhanced MRA Versus DSA for Patients With Extracranial Carotid Stenosis

Reference	Comparator	Sensitivity, %	Specificity, %	Threshold Stenosis	Comment
148	DSA	90	77	Unclear	PCC=0.94
149	DSA	94	??	70%	
150	DSA	86	91	Surgically significant	SCC=0.90
151	DSA	97	82	Degree of stenosis	κ=0.87
109	DSA	92	62	Need for CEA	κ=0.72
152	DSA	93	85	70%	
153	DSA+U/S	94	85	70%	
154	DSA	90–99	90–99	Surgically significant	Meta-analysis

PCC indicates Pearson correlation coefficient; SCC, Spearman correlation coefficient; and U/S, ultrasound.

bolic signals in such cases, thereby giving an indication of the relative risk of the underlying condition. The typical TCD finding is a high-intensity transient signal, which is due to the reflective differences between the flowing blood and the embolic material.[135,136] Some studies have shown an association between increased microembolic signals/high-intensity transient signals during CEA and new brain ischemic lesions postoperatively.[137–141]

Cerebral vasospasm is a common and deadly complication after an SAH. TCD is a useful and noninvasive technique for serial assessment of the development of vasospasm after SAH.[142,143] Flow velocities >200 cm/s, elevated Lindegaard ratios, and a rapid increase in flow velocities all predict a high likelihood of vasospasm.[143,144] The sensitivity and specificity of TCD for the diagnosis of vasospasm vary depending on the vessel being evaluated. The highest detection rates are in the MCA, with sensitivities of up to 90% and specificities ranging from 90% to 100%. Detection of vasospasm in the posterior circulation is less reliable (Table 4).[125,145,146]

TCD has been used to monitor the response of cerebral vessels to thrombolytic therapy, as well as to augment such therapy using ultrasonic energy to enhance clot lysis.[147–149] In general, recanalization and restoration of flow are associated with improved neurological outcomes.[150,151] A recent study reported enhanced clot lysis and improved neurological outcomes when TCD was combined with intravenous tPA therapy.[152]

Sickle cell disease is associated with an increased risk of ischemic stroke in children. TCD has been shown to be extremely useful in monitoring velocities in the intracranial ICA and MCA, where mean maximum velocities of ≥200 cm/s are associated with an increased risk of ischemic stroke.[123,153–156]

In summary, TCD is a safe and noninvasive technique for imaging the intracranial vasculature for some types of cerebrovascular disease, particularly vasospasm and sickle cell disease (LOE: A). Its accuracy is less than that of CTA and MRA for steno-occlusive disease (LOE: A). It is also used for the detection of emboli from a variety of sources. Its usefulness is limited in patients with poor bony windows, and its overall accuracy is dependent on the experience of the technician and interpreter, as well as the patient's vascular anatomy.

Magnetic Resonance Angiography

Introduction and Methods

MRA is performed in combination with brain MRI in the setting of acute stroke to guide therapeutic decision making.[19] There are several different MRA techniques that are used for imaging cerebral vessels. They include 2-dimensional time-of-flight (TOF), 3-dimensional TOF, multiple overlapping thin-slab acquisition (MOTSA), and CE-MRA. A review of the technical aspects of each of these techniques can be found in prior statements and publications.[157]

Accuracy of MRA

A key clinical issue is the comparative sensitivity and specificity of MRA compared with conventional angiography or carotid ultrasound in the detection of high-grade atherosclerotic or atherothrombotic lesions in the neck and head. MRA is also helpful for detecting other, less common causes of ischemic stroke or TIAs, such as arterial dissection, fibromuscular dysplasia, venous thrombosis, and some cases of vasculitis.[158] For hemorrhagic stroke, MRA may be used to detect intracranial aneurysms and arteriovenous malformations. These are reviewed in more detail below.

A review of prospective studies of nonenhanced MRA used for the detection of extracranial carotid disease (threshold stenosis typically 70%) showed a mean sensitivity of 93% and a mean specificity of 88% with 2-dimensional or 3-dimensional TOF sequences.[157] MRA with gadolinium contrast is rapidly replacing TOF techniques for detecting extracranial carotid stenosis. Recent studies of CE-MRA compared with DSA (with or without carotid ultrasound) have shown specificities and sensitivities of 86% to 97% and 62% to 91%, respectively (Table 5).[159–165] The general consensus is that CE-MRA provides more accurate imaging of extracranial vessel morphology and the degree of stenosis than nonenhanced TOF techniques (LOE: A). CE-MRA is now being performed routinely in some centers to detect arterial occlusive disease, sometimes in the setting of acute ischemic stroke (overall LOE: A).[158,166–169] However, other authors have questioned whether enhanced TOF really offers more than unenhanced imaging to detect stenoses >70%.[170]

Intracranial MRA with nonenhanced TOF techniques has a sensitivity that ranges from 60% to 85% for stenoses and from 80% to 90% for occlusions compared with CTA and/or DSA (sensitivity=100%).[171] Some studies[172] have reported sensitivities and specificities of 90% or more for MRA in detecting stenoses >50% (LOE: B). The diagnostic sensitivity and specificity of intracranial CE-MRA compared with TOF techniques and DSA for intracranial atherosclerotic disease are under active investigation in the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA)

study, which is a currently unpublished substudy of the recently stopped Warfarin versus Aspirin for Intracranial Disease (WASID) trial.[173]

MRA is also used for the diagnosis and serial imaging of cerebral aneurysms, particularly the 3-dimensional TOF technique. Although not a cause of acute cerebral ischemia, and although the clinical presentation of a ruptured aneurysm is usually different from that of acute ischemic stroke, the ability of the various MRA techniques to demonstrate an aneurysm is a reflection of their spatial resolution. In general, MRA can reliably detect up to 90% of intracranial aneurysms.[174] Specifically, MRA can detect up to 99% of aneurysms >3 mm; this declines to 38% sensitivity for those <3 mm.[174]

Craniocervical arterial dissections of the carotid and vertebral arteries can often be detected with MRA.[175–178] CE-MRA may improve the detection of arterial dissections,[158] although there are few large, prospective studies to prove its accuracy versus catheter angiography. Nonenhanced T1-weighted MRI with fat-saturation techniques frequently can depict a subacute hematoma within the wall of an artery, which is highly suggestive of a recent dissection.[179,180] However, an acute intramural hematoma may not be well visualized on fat-saturated T1-weighted MRI until the blood is metabolized to methemoglobin, which may not occur until a few days after ictus.

Overall, CE-MRA has greater sensitivity and specificity than Doppler ultrasound for detecting most types of extracranial cerebrovascular lesions (overall LOE: A). It can also noninvasively detect most significant intracranial vaso-occlusive lesions (LOE: B). CE-MRA is useful for detecting intracranial aneurysms (LOE: A) and extracranial arterial dissections (LOE: B); however, it cannot be used in patients with pacemakers, some metallic implants, and those with allergies to MR contrast agents, and its use is limited in patients with severe claustrophobia.

CT Angiography

Introduction and Methods

The evolution of CT scanners over the past decade from a single row of detectors to multidetector imaging (4, transiently 8, then 16, and now 64 rows of detectors), which results in an ever-increasing speed of acquisition and spatial resolution, is likely the single most important factor accounting for the differences in performance of this technique among published studies.[181–183] A number of authors have addressed the appropriate scanning parameters to optimize the technique.[184–186] In general, CTA has twice the spatial resolution of MRA but only half that of DSA.[187] However, as the number of rows of detectors increases, assuming the use of x-ray tube focal spot sizes of ≤0.5 mm, the spatial resolution of CTA will continue to approach that of DSA.[183,187–189] The postprocessing time of CTA images is similar to that of MRA. Because both CTA and MRA produce static images of vascular anatomy, both techniques suffer relative to DSA for the demonstration of flow rates and direction and collateral input into tissues at risk for hypoperfusion.

Accuracy of CTA

CTA is commonly used for the evaluation of extracranial carotid artery stenosis. A large meta-analysis found it to have a sensitivity >80% and specificity >90% for detecting significant lesions compared with DSA.[118] One study found CTA to have equal sensitivity and specificity (100%) compared with DSA for diagnosing severe carotid stenosis.[190] Another study found that CTA had a sensitivity of 89%, specificity of 91%, and accuracy of 90% compared with DSA for diagnosing carotid lesions of >50% stenosis.[191] A study by Berg et al[192] found that CTA was comparable to DSA for diagnosing significant carotid disease. Leclerc et al[193] compared CTA with DSA and found that CTA correctly determined the degree of stenosis in 88% to 90% of cases with carotid stenosis. The differentiation of a very-high-grade stenosis (*string sign*) from a total occlusion is of importance, because a vessel with a high-grade stenosis can be opened with either surgery or angioplasty plus stenting, whereas a total occlusion, unless hyperacute, cannot. CTA has been found to be highly accurate for detecting such a lumen, although not always as good as DSA.[194] However, in some cases, CTA was more accurate than DSA for determining the degree of carotid stenosis, especially the very-high-grade type.[195] CTA is clearly superior to carotid ultrasound for differentiating a carotid occlusion from a very-high-grade stenosis.[196] In terms of identifying plaque morphology, CTA has only 60% sensitivity for detecting significant plaque ulcerations.[197]

Several studies have found CTA to be very reliable for the detection of intracranial occlusions, with sensitivities ranging between 92% and 100%, specificity ranging between 82% and 100%, and a positive predictive value of 91% to 100%.[20,21,172,198] Specifically for the acute stroke patient, Lev et al[20] have demonstrated that the accuracy of CTA for defining the acute intra-arterial thrombus is close to that of DSA. The published sensitivities of CTA for intracranial stenoses are slightly lower than those for occlusion, ranging between 78% and 100%, with specificities of 82% to 100% and a positive predictive value of 93%.[20,171,172,198]

CTA is superior to TCD in the detection of stenoses and occlusions. Suwanwela et al[199] and Graf et al[200] performed prospective studies of 70 and 103 patients, respectively, and found CTA to be clearly superior to TCD for the detection of intracranial stenotic or occlusive disease, with a high false-negative rate for Doppler ultrasound.[199] Suwanwela et al[199] found that CTA was able to detect MCA stenosis in 81% of patients compared with only 41% studied by TCD, whereas distal M1 or M2 disease was detected in 53% of patients with CTA versus 24% of patients with TCD.

Recent literature suggests that CTA not only has sensitivity and specificity for the detection of intracranial stenosis and occlusion that are nearly equal to DSA in the anterior circulation, but it also has a higher sensitivity and positive predictive value than 3-dimensional TOF MRA for both intracranial stenosis and occlusion, including the petrous and cavernous segments of the ICA. CTA appears superior to 3-dimensional TOF MRA, with a higher sensitivity and positive predictive value than MRA for both intracranial stenosis (MRA=70% and 65%) and occlusion (MRA=87% and 59%).[171] Some studies suggest that CTA may be more accurate than MRA for the detection of stenoses in the posterior circulation when slow flow states are present.[195] In addition, Bash et al,[171] using unblinded consensus readings, found 7 (6%) of 115 false-positive occlusions for DSA in the

posterior circulation arteries and noted that CTA was superior to both MRA and DSA in the detection of posterior circulation stenoses when slow or balanced flow states were present. Hirai et al[172] reported a 13% false-positive rate for occlusion when heavy atheromatous calcifications were present. Skutta et al[198] found that CTA was least accurate for stenosis quantification when extensive atheromatous calcifications were present. In contrast, Bash et al[171] noted the sensitivity and specificity of CTA for stenosis quantification were not compromised by the presence of atheromatous calcifications when appropriate window and level adjustments were made to account for the blooming artifacts that are frequently associated with heavy calcific plaque. The study by Bash et al[171] suggests that it may be beneficial to perform low-pitch or delayed CTA whenever DSA shows a posterior circulation vessel to be occluded. They postulated that this advantage of CTA over DSA was due to the longer scan times necessary to perform the CTA study, which allowed for an estimated 9 to 12 intracranial circulation times per CTA (when single-detector systems were in use) as opposed to the single intracranial circulation time (5 to 7 seconds) encountered during routine DSA. This additional scan time allows more contrast to pass through a critical stenosis to opacify the artery distally.

Recent studies show that CTA may be as sensitive and specific as DSA for the detection and characterization of intracranial aneurysms.[201] Most recent studies comparing CTA and DSA have reported sensitivities and specificities for CTA of >90% to 95% for the detection of aneurysms.[202–206] In some cases, a CTA can detect an aneurysm missed by DSA.[207,208] This ability to detect aneurysms almost as well as or even better than DSA demonstrates the significantly greater spatial resolution of CTA over MRA.

In summary, the available data support the fact that CTA is a safe and accurate technique for imaging most extracranial and intracranial vessels for stenoses/occlusions (LOE: A) and for the detection of many intracranial aneurysms (LOE: A). In general, the accuracy of CTA is equal to or superior to that of MRA in most circumstances, and in some cases, its overall accuracy approaches or exceeds that of DSA (LOE: A). New CT scanners with even more detectors may further enhance the accuracy of this technique in the future. Because CTA requires the use of substantial amounts of intravenous contrast material, its application may be limited in patients with contrast allergies and renal dysfunction.

Cerebral Angiography

DSA remains the gold standard for the detection of many types of cerebrovascular lesions and diseases. Indeed, many of the studies cited above used DSA as the comparator for other imaging modalities. Excellent reviews by Barr and by Culebras et al have summarized many of the technical and clinical issues related to DSA.[209,210] For most types of cerebrovascular disease, the resolution, sensitivity, and specificity of DSA equal or exceed that of the noninvasive techniques.[209–214] This is true for many cases of arterial narrowing, dissection, small arteriovenous malformations, vasculopathies/vasculitides, and determination of collateral flow patterns. One exception is intracranial aneurysms, in which case CTA is equal to or better than DSA for large aneurysms and may in some cases detect small aneurysms missed by DSA, because of its multiprojectional capabilities.[201–208]

DSA is an invasive test and can cause serious complications such as stroke and death. Most large series have reported permanent deficits or death in <1% of DSA procedures.[215,216] The largest series of cases to date reported permanent neurological deficit or death in <0.2%.[217] The use of DSA in patients with a contrast allergy or renal dysfunction is complicated, but DSA can be used with proper medical precautions.

Importance of Vascular Imaging in the Acute Stroke Patient

Progress in the treatment of the acute stroke patient has been very slow, and it is apparent that the use of a simple NECT scan of the brain is insufficient to properly select the best patients for treatment.[4,5] For example, patients with the hyperdense MCA sign, which is indicative of a hard thrombus within the MCA, do not respond well to intravenous tPA and may respond better to intra-arterial therapy.[52,218–220] A similar poor response to the drug and poor outcomes have been found when a proximal occlusion is seen on TCD[221] or CTA.[222] The recent randomized trial of intra-arterial urokinase from Japan (MELT: MCA Embolism Local Fibrinolytic Intervention Trial) demonstrated that the outcome after intra-arterial therapy was influenced by the location of the thrombus.[223,224] A retrospective comparison of intravenous versus intra-arterial tPA in patients with the hyperdense MCA sign demonstrated an improvement in outcome when the intra-arterial technique was used, even though it was started later in most cases (<3 hours for the intravenous group versus <6 hours for the intra-arterial group).[220] Thus, there is very strong justification for vascular imaging of the acute stroke patient at the time of the initial brain imaging study, to triage the patient to the best therapy and to determine prognosis, even if that patient presents within the 3-hour window. This has been the routine practice at a number of institutions, such as the Sims group, for years.[222] The Acute Stroke Imaging Research Group has made such a recommendation,[24] as has the American College of Chest Physicians.[225] However, such a practice, especially in the <3-hour window, requires that there be no undue delay in the administration of intravenous tPA, if that is the therapy of choice, and that there be an endovascular team at the institution to undertake intra-arterial therapy, if that is selected.

Summary

Extracranial Vascular Evaluation

1. It is important to evaluate the extracranial vasculature soon after the onset of acute cerebral ischemia to aid in the determination of the mechanism of the stroke, and thus potentially prevent a recurrence. In addition, CEA or angioplasty/stenting is occasionally performed acutely, which requires appropriate imaging (LOE: B).
2. The major extracranial cerebral vessels can be imaged by several noninvasive techniques such as ultrasound, CE-MRA, CTA, and DSA. Although each technique has certain advantages in specific clinical situations, the noninvasive techniques show general agreement with DSA in 85% to 90% of cases (overall LOE: A).

3. Carotid ultrasound is a good screening technique for imaging the carotid bifurcation and measuring blood velocities, but it has limited ability to image the extracranial vasculature proximal or distal to the bifurcation (LOE: A). The use of carotid ultrasound as the sole test may lead to erroneous determination of the degree of stenosis, which may have implications in terms of medical and surgical therapy (LOE: A). The addition of CE-MRA to the ultrasound evaluation still results in a misassignment to the surgical group in 17% of cases (LOE: B).
4. CE-MRA and CTA appear to be more sensitive and specific, and more accurate, than Doppler ultrasound alone for imaging the extracranial vasculature (LOE: A).
5. DSA remains the optimal technique for imaging the cerebral vasculature, particularly when making decisions about invasive therapies (LOE: A). In addition to providing specific information about a vascular lesion, DSA can provide valuable information about collateral flow, perfusion status, and other occult vascular lesions that may affect patient management. However, DSA is associated with a risk, albeit small (<1%), of serious complications such as stroke or death.

Intracranial Vascular Evaluation

1. Imaging of the intracranial circulation in the patient with acute ischemia in the 3-hour window after ictus is extremely important and may aid in the decision to administer a thrombolytic agent intravenously or have the patient undergo intra-arterial thrombolysis with or without mechanical thrombolysis (LOE: B). However, such imaging cannot unduly delay the administration of the intravenous thrombolytic agent, if that is the therapy of choice. In addition, such early imaging presupposes that an endovascular team is available to initiate intra-arterial therapy.
2. Vascular imaging of the acute stroke patient who is seen >3 hours after ictus is an absolute necessity if intra-arterial therapy is contemplated, to determine whether a thrombus amenable to such therapy is present (LOE: A).
3. Imaging of the acute stroke patient can be accomplished quickly and noninvasively with CTA and MRA. For occlusions of the major vessels at the skull base, these modalities are almost as accurate as DSA (LOE: A).
4. Imaging of chronic stenoses and occlusions can best be accomplished by CE-MRA, CTA, and DSA. CTA and DSA have a higher accuracy in determining the degree of stenosis, with DSA being superior to CTA (LOE: A).
5. Imaging of the intracranial vessels for aneurysms can best be accomplished by CE-MRA, CTA, or DSA. CTA and DSA have a higher accuracy rate than MRA (LOE: A).
6. TCD is useful for monitoring the development of vasospasm in large vessels at the base of the brain (LOE: A) and for determining major occlusive disease in those arteries, although CTA, MRA, and DSA are more accurate for occlusive/stenotic lesions (LOE: A). TCD is also useful for monitoring large brain vessels in patients with sickle cell disease (LOE: A).
7. DSA is still the optimal technique for imaging most types of intracranial vascular lesions, as well as determining patterns of collateral flow (LOE: A).

Recommendations

I. Intracranial Vascular Evaluation
   A. Circle of Willis
      1. Acute large-vessel intracranial thrombus is very accurately detected by CTA, DSA, and MRA. Each of these modalities far surpasses the sensitivity of nonvascular studies such as NECT, FLAIR, or gradient-echo MRI, and they are all recommended (Class I, LOE: A).
      2. A vascular study is probably indicated during the initial imaging evaluation of the acute stroke patient within 3 hours of ictus, if such an evaluation does not unduly delay the administration of intravenous tPA, and only if an endovascular team is available to undertake intra-arterial therapy if that is contemplated on the basis of the findings (Class IIa, LOE: B).
      3. A vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient who presents >3 hours after ictus, especially if either intra-arterial thrombolysis or mechanical thrombectomy is contemplated for management (Class I, LOE: A).
      4. For the detection of vascular stenoses and aneurysms, CTA and DSA are recommended (Class I, LOE: A), whereas MRA is less accurate but can be useful (Class IIa, LOE: A).
      5. Although TCD can be used as a noninvasive technique to detect vasospasm or stenoses due to sickle cell and other arterial diseases (Class IIa, LOE: A), CTA and DSA are more accurate in determining the degree of stenosis and should be used for definitive diagnosis (Class I, LOE: A). MRA is less accurate for such assessment than CTA and DSA but can be useful (Class IIa, LOE: A).
   B. Distal intracranial vessels

For the demonstration of more distal acute branch occlusions, or for evaluation of subacute to chronic stenoses, vasospasm, and vasculitis, DSA surpasses CTA and MRA and should be used (Class I, LOE: A).

II. Extracranial Vascular Evaluation
   A. Evaluation of the extracranial vasculature by ultrasound alone should not be done for assessment of occlusive disease if surgical (CEA) or endovascular (arterial angioplasty and stenting) therapy is contemplated (Class III, LOE: A).
   B. For evaluation of the degree of stenosis and for determination of patient eligibility for CEA or carotid angioplasty and stenting:
      1. DSA is the recommended imaging modality to determine the degree of stenosis (Class I, LOE: A).
      2. Two noninvasive techniques (among ultrasound, CTA, and MRA) can be used, although with less accuracy with regard to the degree of stenosis than DSA alone, which thus may increase the chance of inappropriate therapy (Class IIa, LOE: B).
   C. Although CTA (in the absence of heavy calcifications) and MRA are highly accurate for detecting dissection (CTA likely greater than MRA), DSA remains the gold standard and should be used for definitive diagnosis (Class I, LOE: A).

D. A very-high-grade stenosis (string sign) is most accurately detected by DSA, followed closely by CTA. Either can be useful (Class IIa, LOE: B).

Imaging of Cerebral Perfusion

Prior publications have both compared the technical aspects of various brain perfusion imaging techniques[226] and offered guidelines and recommendations for their clinical application in the evaluation of cerebral ischemia.[227] In this section, we survey and expand on those guidelines in the context of current clinical practice and therapeutic trials, using more recently developed definitions for LOEs (Table 1) and strength of recommendations (Table 2). We focus on a time window greater than 3 hours after ictus, because there is an approved therapy for use within the first 3 hours after an acute ischemic stroke (intravenous tPA) that requires only a plain CT scan, although the use of other parenchymal and vascular imaging tests has also been suggested for a more definitive diagnosis, as needed. However, the potential use of intra-arterial thrombolysis or mechanical thrombectomy after 3 hours requires more sophisticated imaging to select the proper patient population to treat with an acceptable risk-benefit ratio.

Possible Roles for Perfusion Imaging of Acute Stroke

Potential utility for perfusion imaging in acute stroke includes the following: (1) Identification of brain regions with extremely low cerebral blood flow (CBF), which represent the *core* (tissue likely to be irreversibly infarcted despite reperfusion) that is at increased risk of hemorrhage with thrombolysis; (2) identification of patients with at-risk brain regions (analogous to the physiological penumbra, the acutely ischemic but viable tissue at risk for infarction in the absence of reperfusion) that may be salvageable with successful intra-arterial thrombolysis beyond the standard 3-hour window for intravenous drug administration; (3) triage of patients with at-risk brain regions to other available therapies, such as induced hypertension or mechanical clot retrieval; (4) disposition decisions regarding intensive monitoring of patients with large abnormally perfused brain regions; and (5) biologically based management of patients who awaken with a stroke for which the precise time of onset is unknown.[228] Perfusion imaging may additionally be of value in clinical trial enrollment. Promising neuroprotective agents in animal models have performed poorly in humans to date.[229] However, there is a growing literature positing that ischemic, potentially salvageable penumbral tissue is an ideal target for neuroprotective agents, which requires proper patient selection.[230–232]

The potential value of perfusion imaging in determining patient management was well illustrated in the recently published DIAS (Desmoteplase in Acute Ischemic Stroke–phase II) trial. In that study, which used the degree of MR diffusion/perfusion mismatch as an entry criterion to receive an intravenously administered thrombolytic compound based on vampire bat venom, a highly significant difference in good outcome was demonstrated between treated and untreated patients up to 9 hours postictus with a sample size in the tens of patients (LOE: B).[8] By contrast, in the original trial (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study), hundreds of patients were required to demonstrate a smaller benefit of treatment with a 3-hour time window.[2] Although this difference may reflect the inherent efficacy of the drug, it may just as well demonstrate the effect of proper patient selection with sophisticated imaging. Further trials will be necessary to separate these 2 variables.

Additional level B evidence for the beneficial role of mismatch in extending the time window for intravenous thrombolysis beyond 3 hours was published recently with both the DEDAS (Dose Escalation of Desmoteplase for Acute Ischemic Stroke) trial[233] and the German Multicenter Study.[234] As the results of other similar in-progress, prospective, randomized trials become available, including the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET), DWI Evolution For Understanding Stroke Etiology (DEFUSE), MR and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and DIAS phase III, the indications for perfusion imaging of the acute stroke patient, whether with MRI or CT, will likely continue to increase. Indeed, the results of the 7-center DEFUSE study suggest that intravenous tPA can be administered safely and effectively up to 6 hours after stroke onset when MR diffusion/perfusion mismatch is present.[235]

Determining the Penumbra and the Core

The anatomic estimate of the penumbra is clearly dependent on the modality with which it is measured[232,235,236] and how rigorously it is defined. Thus, the penumbra determined by flumazenil positron emission tomography (PET) is unlikely to correspond with that determined by DWI/MRP mismatch.[237,238] Even within a given modality, different parameters will lead to different estimates of the penumbra. For example, multiple studies have found that CBF abnormalities are more useful than mean transit time (MTT) measurements in distinguishing different portions of the penumbra that live or die. This is consistent with the fact that MTT is a measure of circulatory dysfunction. All levels of decreased perfusion do not cause ischemia, because ischemia is the metabolic consequence of the decreased delivery of energy-producing metabolites relative to local metabolic demand.[15,239–242] Animal studies have demonstrated that specific thresholds of decreased CBF are predictive of tissue outcome in stroke. The identification of these thresholds in patients is essential to operationally define the penumbra.[243] With MRI, the presence of a larger perfusion abnormality than the DWI lesion is a qualitative marker for potential infarct expansion, although as currently used, it is not a predictor of how much expansion actually occurs.[244] However, the difficulty in truly quantifying MRP severely restricts its ability to define thresholds that accurately differentiate the core from the penumbra within the zone of abnormally perfused tissue. MRP remains extremely sensitive in identifying regions of abnormal perfusion, which makes it useful as a triage technique for patient management, but its specificity in accurately predicting tissue outcome is poor, and in most cases, but not all, MRP overestimates the final infarct volume (FIV).[245–247] Thus, a number of recent publications have highlighted the need for quantitative determination of the penumbra to predict infarct

growth,[248–250] which may require techniques other than MRP to achieve, as will be discussed.

Some centers rely on the qualitative mismatch between the apparent core and the penumbra for management decisions beyond the 3-hour, and especially the 6-hour, time windows for thrombolysis.[16] Although phase II of the DIAS trial was encouraging, the mismatch concept has yet to be validated in large clinical trials providing level A evidence. Indeed, while awaiting the results of trials such as EPITHET and DIAS-phase III, which were designed to assess the role of core/penumbra mismatch in extending the time window for intravenous thrombolysis, some authors have already cautiously proposed the use of either advanced MR or CT for making treatment decisions in patients not in a clinical trial.[55,251] These authors point to the growing evidence of a relevant volume of salvageable tissue present in the 3- to 6-hour time frame in >80% of stroke patients.[252,253] In fact, salvageable tissue may be present so commonly in patients <3 hours postictus that the value of perfusion imaging may be minimal at these early time points.[252,253] Numerous authors have suggested that MR perfusion/diffusion mismatch is present in at least 50% of patients up to 24 hours after stroke onset.[254–256]

The goal is to determine whether perfusion technology in general provides information that aids in patient management decisions and improves patient outcomes. If so, will this be a qualitative or a quantitative approach? There are a number of perfusion technologies, and it must be determined which modality provides the essential information most consistently and accurately. A systematic evaluation of the literature regarding these modalities is presented.

Techniques of Perfusion Imaging

There are 2 major groups of perfusion methodologies. The older group includes those that use a diffusible tracer, whereas the newer group includes those that use an injected contrast agent that, assuming no break in the blood-brain barrier, is a nondiffusible tracer. The former group is exemplified by single-photon emission CT (SPECT) and xenon-enhanced CT (XeCT) scanning, whereas CTP and MRP are examples of the latter group.

Single-Photon Emission CT

Rationale of Technique

SPECT imaging utilizes an intravenously injected radioisotope, typically technitium-99m (^{99m}Tc), attached to some delivery compound capable of traversing the intact blood–brain barrier and being metabolized by neurons and glia. The radiolabeled compounds are taken up during first passage in proportion to CBF at the time of passage.[257] Imaging is performed during the next few hours after injection.

Method of Performance

The delivery compounds to which the radioisotope, ^{99m}Tc, is attached are hexamethylpropyleneamine oxime (HMPAO) or ethyl cysteinate dimer (ECD). ^{99m}Tc and HMPAO may be combined in-house with commercially available kits in approximately 20 to 30 minutes.[258]

After injection, the compound circulates to and localizes within the brain tissues within 1 minute. Scanning of the brain is performed within a few hours of injection[257] with 2- or 3-headed SPECT imaging systems. Data acquisition begins 5 to 10 minutes after injection and is completed in approximately 5 minutes. Image reconstruction is performed with standard filtered back-projection techniques.

Quantification, Accuracy, and Reliability

Even though absolute quantification is possible, semiquantitative techniques are usually performed by comparing counts of radioactivity in a specific region with counts in a comparable, usually homologous region of the opposite normal hemisphere or in a control area, such as the cerebellum. The assumption that the CBF in the opposite, unaffected hemisphere is normal may be incorrect, particularly in patients with chronic cerebrovascular disease or vasospasm. In addition, in the setting of acute stroke, there may be alterations of CBF in distant territories in the ischemic and nonischemic hemispheres that can produce errors in the calculation of such ratios.[259,260] The accuracy and reliability of SPECT CBF have been evaluated through comparisons with other techniques. The relative CBF (rCBF) measured by ECD-SPECT is linearly related to the rCBF measured with perfusion MRI, which in turn is linearly related to absolute CBF as measured by PET. The volumes of hypoperfused brain measured by HMPAO-SPECT correlated significantly with volumes demonstrated by perfusion MRI (LOE: B).[261–263]

Compared with MR and CT, SPECT is a relatively low-resolution technique. Because of high radioactivity counts, large amounts of data can be acquired rapidly, which makes SPECT relatively insensitive to minor head motion.

Applications in Acute Stroke

Patients With No Thrombolytic Treatment

A number of studies have documented the ability of HMPAO-^{99m}Tc SPECT imaging to demonstrate hypoperfusion associated with acute stroke symptoms.[262–280] The sensitivity of this technique to perfusion abnormalities in acute stroke ranged from 61% to 74% and the specificity ranged from 88% to 98% in 2 blinded, prospective, controlled trials (LOE: A).[276] Imaging findings have correlated with infarct size, severity of neurological deficit, and clinical outcome in patients without treatment and with evidence of spontaneous recanalization (LOE: A, B).[263,267–272,279–282] SPECT predicted infarct size, which correlated significantly with infarct size measured by CT.[272] Severe hypoperfusion in the first 6 to 12 hours after symptom onset highly predicted poor neurological outcome (LOE: A).[267–271,282,283] When performed within 72 hours of onset of symptoms, SPECT imaging better predicted short-term outcome than clinical neurological deficit score; if performed later than this, the improved flow due to spontaneous recanalization caused false-negative results.[267] In the first 6 hours after symptom onset, an rCBF threshold of 0.52 on SPECT imaging was found to discriminate between eventual infarction and viability without thrombolysis (LOE: B).[263] Improvement in perfusion caused by spontaneous recanalization correlated with improved clinical outcome (LOE: B).[263,284]

Several studies have included a minority of patients who received thrombolytic treatment. In 1 such study in which most patients were not treated but a minority received streptokinase, SPECT in the first 48 hours of stroke had a

sensitivity of 79% and a specificity of 95% in locating the infarct site as determined by CT at 7 to 10 days after the stroke.[285] In another series of patients, the majority (>60%) of whom received only heparin therapy, semiquantitative SPECT within 6 hours of stroke had a sensitivity of 82% and a specificity of 99% for eventual fatal ischemic edema when an activity deficit of the entire MCA territory was used as the predictor. By comparison, baseline CT sensitivity was 36% and specificity was 100% with hypoattenuation of the entire MCA territory, and the sensitivity and specificity of various clinical predictors ranged from 36% to 73% and from 45% to 88%, respectively.[286] Similarly, count densities above and below 70% of normal distinguished TIA and stroke, respectively, in the first 6 hours after symptom onset with ECD-SPECT in a group of patients, in which 14 of 82 were enrolled in an intravenous tPA trial[285] (overall LOE of these studies: B).

Patients Treated With Thrombolytic Drugs

In patients treated with intra-arterial thrombolysis, the rCBF threshold for reversibility of ischemia was 0.55, whereas the threshold for the development of hemorrhage after treatment was 0.35.[287] These parameters predicted treatment outcome regardless of the duration of the ischemia, the site of vascular occlusion, patient gender, or thrombolytic drug dosage (LOE: B).[287]

Combined HMPAO- and ECD-SPECT have been used within 3 hours after treatment with intra-arterial thrombolysis. Recanalization resulted in normal or increased activity in a previously hypoperfused area with HMPAO-SPECT. Normal activity on ECD-SPECT was seen in patients who recovered neurologically. Decreased activity with ECD was seen in patients with irreversible neurological injury. When decreased activity with ECD was present along with increased activity with HMPAO, patients developed hemorrhage and severe edema (LOE: B).[288] These observations were explained by the theory that HMPAO uptake reflects tissue perfusion only, whereas ECD uptake reflects both perfusion and cellular metabolism[289] (overall LOE: B).

rCBF measured by SPECT also has correlated with clinical outcome in patients treated with intravenous tPA.[265,279] These studies provide evidence for the critical role of collateral circulation to maintain neuronal viability until treatment is initiated. They support the importance of determining the level of perfusion to ischemic tissue in treatment decision making, rather than merely using the time between onset of symptoms and treatment. Demonstration of the extent of tissue viability could permit prediction of treatment response without regard to time from symptom onset. The level of pretreatment perfusion can predict hemorrhagic potential after thrombolytic treatment, guiding the decision to accept the risk of medical recanalization (LOE: A).[265,266,279,288] Comparisons of pretreatment and immediate posttreatment SPECT may also predict long-term clinical outcome. For example, patients who showed perfusion recovery on ECD-SPECT were significantly more likely to be neurologically unimpaired at 3 months after stroke and to have smaller infarcts on CT than patients without perfusion recovery.[289]

Summary

The advantages of SPECT imaging are that it is easy and quick to perform, requiring only an intravenous injection, and it is available in most radiology departments. Widely available software provides CBF images in 3 orthogonal views. Its semiquantitative measurements are simple and can be performed rapidly. Numerous studies have demonstrated that perfusion measured with SPECT correlates with clinical outcome (LOE: A, B).

The disadvantages of SPECT include difficulty in acquiring the kit to prepare the labeled compound on short notice. The data are physiological and not anatomic, such that correlation with either CT or MR acquired at another time must be performed. Overlaying the SPECT on an anatomic CT or MR substrate may be a time-consuming procedure. Compared with CT and MR, SPECT has low spatial resolution. Because arterial concentration of the radioisotope is difficult to obtain, only semiquantitative analysis, such as radioactivity count comparison in analogous regions, is usually possible. Comparison with activity in another area assumes that CBF in the comparison region is normal, which may be inaccurate. Comparison of studies of different patients, performed on different days, or between different institutions requires the use of assumptions that may lead to errors.

Xenon-Enhanced CT

Rationale of Technique and Method of Performance

Xenon is a biologically inert molecule that is used as an inhaled diffusible tracer during CT scanning to provide a measure of brain perfusion. As the patient inhales a 28% to 33% mixture of inert xenon gas, a steady state of xenon is achieved in the brain parenchyma. The CT density changes within the tissues after xenon gas inhalation are used to calculate quantitative CBF values for each voxel at 6 brain levels by use of the Kety-Schmidt equation. A detailed description of the technique has been reported previously.[290]

Quantification, Accuracy, and Reliability

Both animal and human studies have been performed that have demonstrated a strong correlation between normal CBF values acquired with XeCT and other perfusion techniques, including ^{133}Xe and microsphere embolization.[291–294] Studies in animal models and humans with acute cerebral ischemia indicate that XeCT provides accurate CBF values with mild to severe levels of ischemia.[259,293,295]

Applications in Acute Stroke

Identification of Ischemia in Acute Stroke

Firlik and colleagues[295] retrospectively explored the sensitivity of XeCT in the diagnosis of ischemic stroke in 20 patients with MCA territory occlusions who presented within 6 hours of onset and correlated XeCT abnormalities with angiographic findings. In this select population of patients, noncontrast CT scans were abnormal in 55% of patients, and XeCT scans were abnormal in 100% of patients. In the 15 patients who underwent angiography, a mean CBF in the affected vascular territory <20 mL $\cdot$ 100 g^{-1} $\cdot$ min^{-1} was 91% sensitive and 100% specific for an M1 occlusion.

Rubin and colleagues[296] documented transhemispheric diaschisis in the setting of acute cerebral ischemia. They retrospectively analyzed XeCT CBF values in 23 patients studied within 8 hours of symptom onset. The mean CBF in the unaffected hemisphere was 35% less than the normal

mean value and was also significantly decreased in the ipsilateral cerebellum.

Prediction of Prognosis and Clinical Outcome

Rubin et al[297] retrospectively analyzed XeCT findings obtained within 8 hours of symptom onset in 50 patients with hemispheric stroke. CBF values in the symptomatic vascular territory were compared with the contralateral homologous region and correlated with discharge National Institutes of Health Stroke Scale (NIHSS) scores. They found that mild CBF asymmetry (≤20%) correlated with good neurological outcome, whereas severe asymmetry (≥60%) correlated with poor outcome. Outcomes in patients with CBF asymmetries in the range of 20% to 60% were variable.

In the previously cited study by Firlik et al of acute MCA territory strokes imaged within 6 hours of symptom onset with XeCT,[295] they found that a mean CBF of 15 mL · 100 g^{-1} · min^{-1} or lower was significantly associated with the development of severe brain edema and herniation. Sensitivity and specificity of this threshold were 89% and 63%, respectively, for severe edema and 100% and 50%, respectively, for herniation.

In another retrospective analysis, Firlik and colleagues[298] explored whether XeCT CBF measurements could distinguish patients with transient deficits from patients with evolving strokes. They studied 51 patients with acute hemispheric stroke symptoms who underwent XeCT within 8 hours of symptom onset. All 8 of the patients whose deficits resolved without thrombolytic therapy had normal CBF values compared with 42 of 44 patients whose deficits did not resolve and who had abnormal CBF values.

Kilpatrick and colleagues[299] subsequently explored whether XeCT alone or in combination can be used to predict new infarction and functional outcome. They retrospectively identified 51 patients with hemispheric stroke symptoms who underwent CT, CTA, and XeCT within 24 hours of symptom onset at their institution. They found that patients with no infarction on initial CT and normal XeCT CBF had significantly fewer new infarctions and were more likely to be discharged home than those with compromised CBF.

Prediction of Irreversible Ischemia and FIV

Kaufmann et al[300] explored whether CBF thresholds could be identified that predict FIV. They retrospectively analyzed XeCT images from 20 stroke patients with MCA occlusions imaged within 6 hours of symptom onset. In the 12 patients with follow-up CT scans available (obtained between 2 and 41 days after onset), a significant correlation was found between the extent of severe ischemia with CBF ≤6 mL · 100 g^{-1} · min^{-1} and the area of final infarction (Pearson correlation coefficient=0.866). Of note, some patients were treated with intra-arterial thrombolytic therapy.

Rubin and colleagues[301] retrospectively analyzed XeCT findings in 10 patients undergoing thrombolytic (either intravenous or intra-arterial) therapy for acute hemispheric ischemic stroke within 6 hours of symptom onset. In the 9 patients with partial or complete recanalization at angiography after thrombolysis, the follow-up XeCT showed reperfusion of the ischemic brain areas. However, regions with CBF of 0 mL · 100 g^{-1} · min^{-1} at baseline demonstrated infarction on follow-up imaging despite reperfusion.

Jovin et al[302] retrospectively studied XeCT values in 36 patients with MCA stem occlusions imaged within 6 hours of symptom onset; 11 patients were treated with thrombolytic therapy. Using CBF thresholds identified from prior studies, they found marked variability in the percentage of core tissue present but a relatively consistent percentage of penumbra present. However, only the percentage of core present was significantly associated with clinical outcome.

Use of XeCT to Guide Acute Stroke Treatment

The above studies suggest that XeCT has the potential to predict both tissue and clinical outcome in acute stroke, particularly in the subset of patients with large-vessel anterior circulation occlusions. Although it has been proposed that this information, particularly in combination with data from noncontrast CT and CTA, could be useful in therapeutic decision making, no prospective study has been performed to date to test this hypothesis.

Summary

There is a paucity of primary research articles related to XeCT imaging in acute stroke in the literature. The majority of reports have been generated from a single center, with overlap of patients across studies. Most reports were retrospective analyses, generally without a control group available. Additional limitations include small sample size and the use of select patient populations. The LOE across all studies ranges from level C to level B. Current data support the diagnostic accuracy of XeCT for determining quantitative CBF values in acute stroke. Although retrospective case series support the use of XeCT to improve efficacy in diagnosis and therapeutic management, prospective validation studies are needed to demonstrate this. No data exist to date that address the role of XeCT to improve patient outcome or to show its cost-benefit ratio in treatment. An important task for future research will be to compare the clinical utility of XeCT in combination with NECT and CTA with multimodal MR and multimodal CT approaches.

CT Perfusion

Rationale of Technique

In the emergency assessment of acute ischemic stroke, the complete CTP examination has 3 components: (1) NECT, (2) vertex-to-arch CTA, and (3) dynamic first-pass cine CTP, performed over 1 or 2 slabs of tissue.[20,21] Importantly, the source images from the whole-brain CTA vascular acquisition (CTA-SI) provide clinically relevant data concerning tissue-level perfusion. Assuming an approximately steady state level of contrast in the intracranial arteries and capillaries, CTA-SI is predominantly CBV weighted rather than CBF weighted.[303–305] Although the CTA-SI images can be viewed qualitatively, coregistration and subtraction of the conventional NECT brain images from the CTA-SI images results in quantitative blood-volume maps of the entire brain.[305–307] The subsequent dynamic CTP examination with cine acquisition measuring the first pass of a contrast agent in 1 or 2 regions of interest (tissue slabs) produces quantitative CBF, MTT, and CBV maps.

Method of Performance

Data Acquisition

CTA with CTP is fast,[20] increasingly available,[306] safe,[308] and affordable.[309] It typically adds no more than 5 minutes to the time required to perform a head NECT and does not delay intravenous thrombolysis, which can be administered, with appropriate monitoring, directly at the CT scanner after completion of the NECT.[20,21,71,306,308,310–334] Immediate interpretation of the vascular anatomy is aided by reformatting the images in thick (2 cm) axial, coronal, and sagittal sections.

The following is a typical sample protocol: An 18- or 20-gauge cannula is positioned in an antecubital vein; patients are monitored during scanning, which enables intravenous thrombolysis to be started on the CT table after the NECT is completed through a separate intravenous catheter (which is important to avoid inadvertent rtPA administration). CTA is acquired immediately after NECT, from the vertex to aortic arch, with semiautomated threshold-based triggering of the administration of 105 mL of low-osmolar, nonionic contrast agent, infused at 4 mL/s with a saline push power injector. Dynamic CTP is performed next, which requires an additional 45 to 60 seconds of scanning time, as well as an additional 40 to 50 mL of contrast per slab over what is needed for CTA. This small contrast bolus is administered at 4 to 7 mL/s during continuous cine imaging over a single brain region that is started 5 seconds after the start of the infusion. With most scanners, 2 to 4 cm of coverage per bolus is obtained (5- or 10-mm-thick slices).[310,313,322] Some centers routinely obtain 2 slabs, which requires an additional bolus of 40 mL of contrast, to double the coverage, as advocated by Wintermark et al.[333] Although CTP can be performed on even early-generation multidetector CT scanners, the newer 16- and 64-slice machines provide faster, more complete coverage. Imaging parameters are 80 kilovolts (peak) [kVp], 200 mA, and 1-second rotation time. At least 1 imaged slice must include a major intracranial artery for CTP map construction. The scan plane is angled along the superior orbital roof. CTA-SI data are available immediately before the CTP acquisition, to locate the region of abnormal perfusion and to guide the choice of imaging plane through that region.

Contrast Safety and Radiation Dose Considerations

Unlike DWI/MRP, CTA/CTP requires ionizing radiation and iodinated contrast. The safety issues involved are no different from those of any patient group receiving contrast-enhanced head CT scanning.[307,310,335] The recommended scanning parameters for CTP (specifically, 80 kVp and approximately 200 mA) have been optimized to provide maximal perfusion signal with minimal radiation dose.[310] It has been estimated that a 2-slab CTP deposits only a slightly greater radiation dose than a routine unenhanced head CT, or approximately 3.3 mSv.[310,336] Hardware and software innovations have the potential to further reduce this dose to as low as 0.85 to 1.85 mSv with currently available scanners and postprocessing tools.[337]

Modern iodinated CT contrast agents have been shown not to worsen stroke outcome.[338–340] Most centers performing stroke CTA/CTP call for the use of low or iso-osmolar contrast to minimize the risk of contrast-induced nephropathy. It has been suggested that iso-osmolar contrast agents (≈300 mOsm) have an improved safety profile over that of high-osmolar contrast agents, even for high-risk diabetic patients with baseline creatinine of ≈1.9 mg/dL (range 1.5 to 3.5 mg/dL) who are undergoing high-dose procedures such as aortofemoral angiography.[341] It has additionally been suggested that low-osmolar contrast agents (<600 to 800 mOsm) have a similar safety profile.[342] The mainstay of contrast-induced nephropathy prevention is adequate preprocedure and postprocedure hydration, up to 12 hours before and after contrast administration, if possible, especially given that mannitol and diuretics have not proved beneficial in the prevention of contrast-induced nephropathy.[343]

Reconstruction and Postprocessing

Although postprocessing of CTA and CTP images is more labor intensive than that of MRA and MRP, with training and quality control, 3-dimensional reconstructions of CTA data sets, as well as quantitative CTP maps, can be constructed rapidly and reliably.[344–346] Indeed, newer-generation CTP reconstruction software holds the promise of being truly turn-key (M.H. Lev, written communication, December 2005). Moreover, because CTA-SI maps consist only of the raw data from the CTA acquisition, no postprocessing is involved.[20,72,73,347]

The first-pass CTP cine source images are transferred to a freestanding workstation and analyzed with commercially available deconvolution-based software to create quantitative maps of CBF, CBV, and MTT. The deconvolution-based software requires the user to select multiple input variables. In 1 small study, major variations of either arterial region-of-interest placement or arterial and venous region-of-interest size had no significant effect on the mean CBF, CBV, and MTT values at the infarct core ($P<0.05$). Even minor variations, however, in the choice of venous region of interest placement or in preenhancement and postenhancement cutoff values significantly altered the quantitative values for each of the CTP maps by as much as 3-fold.[346] Awareness of these results by clinical imagers may be important in the creation of quantitatively accurate CTP maps.

Quantification, Accuracy, and Reliability

CTP Image Review

Eastwood et al[334] showed good κ-Pearson correlation between readers for extent of CBF abnormality (0.94, $P=0.001$); intraobserver variation was 8.9% for CBF abnormalities. In another study, raw data derived from dynamic CTP examinations performed in 20 subjects were postprocessed 7 times by 3 experienced CT technologists.[344] The authors concluded that although there was a high degree of correlation between parenchymal regions of interest derived from CTP maps generated from the same dynamic source data postprocessed by different operators, the level of agreement may not be sufficient to incorporate quantitative values into clinical decision making. It is likely, however, that with optimization of postprocessing parameter selection, the degree of variability may be reduced substantially.[344] There have been continued efforts toward the development of practical automated and semiautomated imaging tools for interpretation of CTP images.[347] CTP software is being distributed with new CT scanners, and is being used as part of

the phase III DIAS trial in which mismatch between CTP and the noncontrast CT abnormality is a selection criterion.

CTP Validation and Penumbral Measurement

The creation of accurate, quantitative CTP maps by the deconvolution method has been validated in a number of studies.[313,321–323,332,348–351] Specifically, validation has been accomplished by comparison with XeCT,[332,352] PET,[353] and MRP,[69,354–357] both in humans and with microspheres in animals.[313,321,323] However, 1 study found the correlation between MRP and PET perfusion values to be less reliable than expected.[358] CTP has greater spatial resolution than MRP and more readily lends itself to quantification. MRP may also be more sensitive to contamination by large vascular structures. These factors may contribute to the possibility that visual assessment of core/penumbra mismatch is more reliable with CTP than with MRP.[359,360] Of note, if vascular pixels are excluded from the calculation of CT-CBF, quantification of mean CBF is highly accurate compared with values obtained with $H_2{}^{15}O$ PET.[361]

Applications in Acute Stroke

Tissue Outcome

CTA-SI

It has been hypothesized that CTA-SI, like DWI and CBV, can specifically detect infarct core (ischemic regions likely to be irreversibly infarcted despite recanalization) and can therefore be used to define a worst-case lower limit to final infarct size.[21,72,311] Also, like DWI, a time-dependent threshold for these blood volume changes has been observed, and reversal can and does occur in the setting of early complete recanalization.[65,362,363] CTA-SI is important for the CT evaluation of stroke, because as opposed to quantitative CTP, it is a series of images of the whole brain and hence may be useful in extrapolating regional tissue CTP models to the entire brain.

In a study of 22 consecutive patients with MCA stem occlusion who underwent intra-arterial thrombolysis within 6 hours of stroke onset, it was found that with early complete recanalization, CTA-SI lesion volume approximated that of the follow-up scan, whereas in the absence of recanalization, there was significant lesion growth. Moreover, an admission CTA-SI lesion volume of <100 mL (coincidentally, approximately one third the volume of the MCA territory) reflected the break point between patients expected to have a good or fair outcome on follow-up modified Rankin score (depending on degree of recanalization) versus poor outcome despite complete recanalization (those with a volume >100 mL). The strength of the association between CTA-SI lesion volume and outcome was stronger than that between NIHSS score and outcome.[21]

A more recent study of 37 consecutive anterior circulation stroke patients imaged <6 hours after ictus has confirmed and expanded on these results. In patients with major reperfusion, mean CTP-CBV and CTP-SI infarct size closely predicted final infarct size; review of the CTP source images was more accurate at identifying the extent of reversible and irreversible ischemia and at predicting final clinical outcome than review of the unenhanced CT or CTA-SI.[347]

CT Perfusion

A recent study sought to determine whether CTP-CBF thresholds for distinguishing benign oligemia from nonviable penumbra could be established.[247] The authors studied a homogeneous population of 14 intra-arterial lysis patients within 8 hours of stroke onset, performing separate region-of-interest analyses for gray versus white matter, and reported both relative and absolute threshold results. They concluded that normalized or relative CTP-CBF (rCBF) is the most robust parameter for distinguishing benign oligemia from nonviable penumbra (assuming that the normalization accounts for the variable gray-to-white matter ratio within the ischemic region of interest, because gray and white matter have different baseline CBF values, a conclusion that has recently been underscored in the MRI literature as well[364]). When the recanalization versus no-recanalization groups were compared, ischemic regions with >66% reduction in CTP-CBF, normalized to contralateral mean values, had >95% positive predictive value for infarction (95% specificity), despite the presence of robust recanalization, and ischemic regions with <50% reduction in CTP-CBF had >90% positive predictive value for survival (95% sensitivity), despite the absence of robust recanalization.[247]

These preliminary thresholds—>66% reduction in CBF for nonviable penumbra and <50% reduction in CBF for benign oligemia—may predict the upper and lower limits of final infarct size in a more precise manner than is currently possible with DWI/MR-MTT mismatch. Additionally, the authors found that the visual threshold for identification of the CTP-CBV core corresponded to a 75% reduction in CTP-CBF.[247] The visually evident CTP-CBV lesion (along with the CTA-SI lesion) is therefore likely to infarct, because it is associated with CTP-CBF reductions below the threshold for nonviable penumbra. Another recent study has suggested a quantitative threshold of CBV <2 mL/100 g as being highly accurate for determination of infarct core, and a relative CTP-MTT increase of >150% as being accurate for defining the at-risk penumbra.[365]

Clinical Outcome: CTA/CTP

The penumbra is dynamic, and several factors influence its fate, including time since stroke, residual and collateral blood flow, admission glucose, temperature, hematocrit, systolic blood pressure, and treatment, including normobaric hyperoxia.[366] It is technically challenging to measure the penumbra. Despite this, a number of consistent messages emerge from a review of the literature regarding outcome prediction in acute ischemic stroke with various imaging parameters. One such message is that a determination of the volume of the core is critical. In cases of successful recanalization, multiple studies have found that clinical outcome is strongly correlated with admission core lesion volume, be it measured by DWI, CTP-CBV, CTA-SI, XeCT-CBF, or unenhanced CT.[302,367–371]

A second is that bolus-tracking techniques, such as dynamic MRP, sensitively identify the region at risk for infarction, correlate better than core with admission NIHSS, but in general overestimate the final infarct and lack specificity.[248–250] In a recent study, the correlation between the degree of MR diffusion/perfusion mismatch volume and DWI expansion was not found to be statistically significant.[244] Like DWI/MRP imaging,

CTA-SI/CTP has the potential to serve as a surrogate marker of stroke severity, possibly exceeding the NIHSS or ASPECTS scores as a predictor of outcome.[44,45,51,230,311,372–375] A report suggested that multimodal CT evaluation improves detection rate and prediction of the final size of infarction compared with NECT, CTA, and CTP alone.[376] Nabavi et al,[377] using a very simple approach, were able to create a surprisingly accurate CTA-SI/CTP–based stroke scale score predictive of NIHSS, called the MOSAIC (Multimodal Stroke Assessment Using Computed Tomography) score. The MOSAIC score, a number ranging from 0 to 8 that reflects the sum of the scores for these components, was a stronger predictor of final clinical outcome at 3 months (modified Rankin score and Barthel Index) than were any of the individual components alone, or the NIHSS score.

Evidence Supporting the Use of CTP in Acute Stroke Imaging

Many of the studies cited in this section reflect level C evidence, with some of the larger prospective trials being of B level.

Summary

Compared with MRP, CTP has advantages of speed, low cost, and most importantly, widespread availability. CTP parameters of CBV, CBF, and MTT can be more easily quantified than their MRP counterparts, owing in part to the linear relationship between iodinated CT contrast concentration and resulting CT image density (expressed in Hounsfield units), a relationship that does not hold for gadolinium concentration versus MRI signal intensity. However, as with other bolus-tracking techniques, quantification is dependent on the deconvolution method to calculate CBF based on a comparison of the tissue curve with the arterial input function. Because of its availability, simpler methodology, and greater degree of quantification, CTP has the potential to increase patient access to new treatments and imaged-based clinical trials. Pilot studies have suggested that the mismatch between ischemic lesion size on admission CTP-CBV (or CTA-SI) and CBF maps can be used much like MR DWI/MRP mismatch to operationally identify salvageable brain tissue in the acute stroke setting. CTA also has the potential to rapidly and accurately localize the vascular source of stroke to identify appropriate candidates for recanalization. In addition, hypodense regions on the source images from the CTA (CTA-SI) reflect reduced CBV that denotes tissue that is difficult to salvage with reperfusion (core). These CTA-SIs cover the entire brain volume, require no postprocessing, and are available immediately at scan completion.

A current disadvantage of CTP is limited coverage, typically a 2- to 4-cm-thick slab per contrast bolus depending on the manufacturer and the generation of multidetector CT scanner used. The many contraindications to MRP in acute stroke patients, such as difficulty scanning patients on monitors or ventilators, presence of pacemakers or implantable defibrillators, aspiration with long periods supine, and inability to obtain a history to rule out metallic implants, do not exist with CT.

The ultimate goal of acute stroke treatment is to minimize neurological deficit and maximize functional outcome. Because of the superior quantitative capability of CT, as opposed to MRP imaging, application of specific CTP CBF and CBV thresholds to predict tissue survival or infarction appears promising. Because smaller studies have suggested that the calculated volume salvaged by reperfusion is correlated with improvement in NIHSS, it is essential that these thresholds be validated in larger patient cohorts for which reperfusion status is known.

MR Perfusion

Rationale of Technique

Preliminary studies exploring the use of perfusion-weighted MRI (PWI, or MRP, which has been used throughout the present statement) in acute ischemic stroke have suggested its utility in predicting lesion growth and clinical outcome. Baird et al[378] demonstrated that most patients with a perfusion/diffusion mismatch (hypoperfusion volume greater than DWI ischemic lesion volume) have a significant increase in infarct volume over time if no increased perfusion occurs, whereas patients without a mismatch have no subsequent growth in infarct size. Without recanalization, baseline volumes of hypoperfusion were found to have better correlation with the size of the final infarct than baseline lesion volumes on DWI.[379,380] Particularly in the hyperacute setting, an ischemic region on MRP may be present even in the absence of an acute lesion on DWI, which further emphasizes the potential utility of MRP in identifying tissue at risk.[379] Baseline volumes of hypoperfusion by MRP have also been shown to correlate better with clinical scales at baseline or outcome than do lesions on baseline DWI.[379–381] Investigations of the best MRP analytical method focus on identifying the highest correlation of ischemic volume with acute clinical deficits (symptomatic hypoperfusion) or with the volume of the infarct that becomes defined over time (tissue at risk).

Method of Performance

Magnetic susceptibility effects, as defined by the MR parameter T2*, are due to metals, blood products, air, and other substances that produce local magnetic field variations or gradients, which lead to proton dephasing and intravoxel signal loss. After a contrast agent containing a heavy metal, such as gadolinium or dysprosium from the lanthanide group, is injected into the bloodstream, it passes rapidly through the microvasculature to produce local signal loss equal to the size of the blood vessel and usually an additional capillary radius beyond that vessel. Gradient-echo imaging is particularly effective at detecting T2* effects, and a high-speed, multislice gradient-echo technique that uses a single radiofrequency input or shot, such as echoplanar imaging, is capable of obtaining thin imaging slices through the entire brain every second that are T2* sensitive.[382,383]

Typically, images are obtained every 1 to 2 seconds. Baseline images without contrast are acquired over approximately 40 seconds before the injected contrast agent arrives, followed by sequential imaging over the next minute as the contrast moves rapidly through the vasculature. Signal intensity–versus-time curves can be determined for each voxel. Theoretically, the area under the curve closely approximates CBV, whereas the full width of the curve at one half of its maximum value (FWHM) is proportional to MTT. The ratio of the 2 yields CBF. These are all relative values, because the signal intensity is not linearly related to the volume of contrast in the vasculature (in CTP, there is a linear

relationship to the density measured by the CT scanner and the volume of the iodinated contrast agent in the vasculature). For more accurate quantification, an arterial input function is a necessary component, but this is not an easy parameter to measure with MR. Direct determination of the concentration of the paramagnetic contrast agent in a small vessel such as an MCA is not trivial, and it is difficult to measure the signals from a large vessel such as the ICA that may be outside the scanning volume. However, there are mathematical models that allow the arterial input function to be deconvolved from the tissue concentration–versus-time curve to estimate the arterial input function and produce multiparametric perfusion maps, similar to the methods used for CTP.[54,382,383]

As with CTP, the echoplanar imaging data are transferred to a separate workstation on which the perfusion maps are produced. Data derived from the diffusion-weighted sequence are used to construct apparent diffusion coefficient maps. These diffusion and perfusion maps are then compared to produce a perfusion/diffusion map, to look for a mismatch that might indicate the presence of ischemic but salvageable tissue.

The major advantages of MRP over CTP include whole brain coverage, speed of acquisition of many data points per voxel, and its inclusion in a package of imaging sequences that effectively evaluate many aspects of the parenchyma, including the presence of ischemia with DWI. The vasculature can also be evaluated with MRA. The disadvantage is the lack of linearity between signal intensity and contrast concentration, which makes quantification very difficult, and thus, no absolute value of perfusion is available for clinical decision making. Instead, regions of interest on relative maps must be compared as surrogates for absolute data.[54,382,383]

Relative Quantification, Accuracy, and Reliability

Preliminary Studies Evaluating MRP Thresholds

To achieve the goal of predicting infarct evolution and clinical outcome, different thresholds of MRP parameters have been proposed to identify tissue at risk of infarction. Acute hypoperfusion volumes derived from a variety of analytical approaches have been found to be predictive of tissue outcome. Schlaug et al[243] found that a reduction in initial relative CBV (rCBV) to 47% of the contralateral control region and a reduction in rCBF to 37% of the contralateral control region characterized the ischemic penumbra, which they operationally defined as the region between the initial diffusion abnormality (core) and its extension as seen on the 24- to 72-hour follow-up DWI study. A more severe reduction in these perfusion parameters was proposed as the threshold that fit the ischemic core. Other groups have proposed different MRP thresholds to differentiate ischemic penumbra from benign oligemia or ischemic penumbra from core. Neumann-Haefelin et al[254] found that a time to peak (TTP) delay of ≥6 seconds was predictive of lesion enlargement at 6 to 10 days after stroke, whereas Parsons et al[384] and Thijs et al[385] found that MTT delays between 4.3 and 6.1 seconds and >4 and <6 seconds, respectively, predicted tissue that progressed to infarction. Shih et al[386] instead sought to differentiate irreversibly infarcted core tissue from penumbral tissue despite early recanalization by thrombolysis. Using an adjusted TTP of the residue function (T_{max}), they found that T_{max} ≥6 and ≤8 seconds correlated best with FIV at day 7.

Which MRP Method Is the Most Accurate?

Further investigations of perfusion MR in larger series of patients have continued to demonstrate that these different MRP methods are, on the whole, predictive of FIV and clinical outcome, variably defined; however, they have not resulted in a consensus as to which perfusion parameter is the most accurate predictor of tissue fate and clinical outcome. Individual centers have prospectively accumulated their own case series and retrospectively analyzed the imaging data with different perfusion postprocessing techniques. Thus, CBF, MTT, TTP, and CBV parameters may not be directly comparable between studies because different analytic models have been used to derive nominally the same parameter, and different image-acquisition techniques (eg, spin echo versus gradient echo) have been used. Furthermore, patients studied have varied both within and between reports with respect to vessel status, ie, recanalization versus persistent occlusion, or thrombolytic treatment, factors that could affect stroke evolution and thus the evaluation of MRP as a predictor of stroke outcome. All of these variations have made it difficult to compare the relative accuracy of the methods, and direct comparisons of different methods on the same sample of patients are lacking. Notwithstanding the lack of a validated best method, a variety of perfusion MRI techniques (eg, CBF, CBV, and MTT) reveal volumes of hypoperfused brain that correlate variably with clinical severity and outcomes. The following review includes studies with sample sizes of >30 patients to summarize the current state of knowledge of the utility of perfusion MR in acute stroke.

1. MRP Volumes as Predictors of FIV and Outcome. Schellinger et al,[387] in studying 51 acute stroke patients with MRI within 6 hours of symptom onset, almost half of whom received thrombolytics, found only a small correlation between acute diffusion and perfusion lesion volumes and both acute and day 90 NIHSS scores. For DWI, these correlations were better in the subgroup of patients who had recanalized by day 2 than in those who had not, whereas the opposite was true for MRP. In that study, MTT perfusion maps were calculated as the normalized first moment of the concentration/time curve. On the basis of their findings, they concluded that hyperacute DWI and MRP may not represent the true baseline or severity of clinical outcome but instead the potential best-case (and worst-case) scenarios, depending in part on early recanalization.

However, many other groups have found a strong correlation between acute MRP values and clinical outcome, as well as FIV, although imaging was often performed up to 24 to 48 hours after symptom onset in patients who did not receive thrombolytics. Karonen et al[261] compared MRP rCBF maps, correlated to SPECT as the reference standard of measuring CBF, and FIV, defined as DWI lesion volume at 1 week, in patients who did not receive thrombolytics. In 46 patients, half of whom also underwent SPECT, they found that acute MRP volumes of hypoperfusion had a statistically significant correlation with FIV and with acute SPECT

hypoperfusion volumes performed on the same day as the MRP. In a subsequent study,[280] they compared different MRP parameters (rCBV, rCBF, and MTT) with the FIV in 49 patients, none of whom had received thrombolytics. All of the MRP maps correlated significantly with the FIV. The best correlation was found with the initial rCBV volume, whereas the rCBF and MTT maps tended to overestimate the final infarct. Schaefer et al[388] and Kluytsmans et al[389] also found rCBV to be the best predictor of FIV when comparing different MRP parameters in patients who had not received thrombolytics. The presence of an rCBV-DWI mismatch was also the best predictor of lesion growth compared with an rCBF-DWI or MTT-DWI mismatch.[278,388,389] Furthermore, rCBV correlated better with clinical outcome, measured by 4-month NIHSS, modified Rankin scale, and Barthel index, than did MTT.[389] The presence or absence of spontaneous recanalization was not assessed in these studies.

2. Is There an MRP Threshold Value That Is Most Predictive of Lesion Growth and FIV? Different groups have used different perfusion mapping techniques in an attempt to retrospectively identify a perfusion threshold that best predicts final infarct size on follow-up T2-weighted imaging, although again, there is no consensus on which threshold to use. In evaluating different thresholds of perfusion delay on TTP maps of 50 stroke patients within 24 hours of symptom onset, Wittsack et al[390] found through volumetric analysis that a TTP delay >6 seconds best correlated with final infarct size as measured on days 6 to 11 and was particularly useful <4 hours after symptom onset, when DWI was less reliable in demonstrating the full extent of the ischemic territory. Although other perfusion maps were calculated, they were not included in the volumetric analysis. Butcher et al[17] explored potential thresholds for infarcted versus salvageable tissue on MTT, rCBF, and rCBV maps in 35 patients, half of whom were treated with intravenous thrombolysis. Evidence of reperfusion was also assessed. They found a difference in relative MTT and rCBF values, but not rCBV, in infarcted versus salvaged tissue, although there was significant overlap. Furthermore, early reperfusion allowed more severely hypoperfused tissue to be salvaged. Therefore, an absolute perfusion threshold could not be demonstrated with any of the techniques studied, because the perfusion thresholds for infarction depended on time to reperfusion.

Thomalla et al[234,391] chose to use a TTP delay of >4 seconds ($TTP_{>+4s}$) to retrospectively identify a perfusion volume threshold within 6 hours of symptom onset that could predict the development of malignant MCA infarction. A $TTP_{>+4s}$ >162 mL had 83% sensitivity and 75% specificity for predicting malignant MCA infarction. Fiehler et al[392] chose instead to evaluate a CBF threshold of $\leq 12\ mL \cdot 100\ g^{-1} \cdot min^{-1}$ (CBF_{12}), derived from the PET literature, and found that a relative CBF_{12} tissue volume ≥50 mL within 6 hours of symptom onset was predictive of further lesion enlargement.

Although different absolute perfusion thresholds and perfusion volume thresholds have been correlated with FIV and lesion growth, the best method has yet to be identified. However, time to reperfusion will be an important factor to take into consideration when this determination is being made.

Applications to Acute Stroke Therapy

Because MRP provides important pathophysiological information in acute stroke, MRP in concert with DWI has the potential to guide patient selection for acute stroke treatment and serve as a potential imaging surrogate end point in clinical trials. It is understood that although they are based on physiology, these imaging techniques provide an operational methodology at a given point in time for patient selection to a management protocol. For this purpose, the simplest model of the tissue at risk, the qualitative diffusion/perfusion mismatch, which is highly predictive of lesion growth, may be adequate.[256,378]

Through their retrospective analysis, Derex et al[393] suggested the use of MRP and DWI along with site of vessel occlusion to guide treatment. They obtained MRIs in 49 patients within 6 hours of symptom onset before intravenous thrombolysis; 47 of these patients had an intracranial large-vessel occlusion by MRA, and patients with extracranial ICA stenosis were excluded. TTP maps were used to measure perfusion lesion volumes. Patients with intracranial ICA occlusion had significantly larger pretreatment perfusion defects and perfusion/diffusion mismatch volumes. Differences in rCBF and peak height values between the ischemic focus and an analogous region in the contralateral hemisphere were also significantly higher in patients with intracranial ICA occlusions than in those with more distal occlusions, whereas MTT, TTP, and CBV difference values did not distinguish among the sites of arterial occlusions. Patients with intracranial ICA occlusions also had a lower recanalization rate after thrombolysis than those with more distal occlusions, and they had worse clinical outcomes. The hemodynamic information gained from acute MRI, including perfusion and site of vessel occlusion, could be used to identify patients in whom intra-arterial therapy alone or combined intravenous and intra-arterial therapy may be necessary to achieve recanalization. Sunshine et al[238] applied this use of multimodal MRI prospectively for treatment selection in 35 patients within 6 hours of symptom onset. Patient management was guided primarily by evidence of large-vessel occlusion; in addition, the treatment of 2 patients was determined by the demonstration of hyperperfusion on MRP, and these patients were managed conservatively.

In addition to having the potential to identify appropriate patients for treatment, MRP along with DWI has been used as a surrogate marker of outcome in phase II trials to signal efficacy. With the use of serial MRIs, including MTT maps with a threshold delay >4 seconds, Barber et al[394] demonstrated in 49 acute ischemic stroke patients that major reperfusion and infarct expansion are associated with clinically significant changes in outcome. On the basis of their results, they calculated theoretical sample sizes that would be necessary for phase II stroke therapy trials to demonstrate proof-of-concept to determine whether a larger phase III trial should be pursued.

An early reperfusion response on MTT has been found to be predictive of clinical recovery with standard intravenous tPA therapy. Chalela et al[395] found that the strongest independent predictor of excellent outcome in multivariate logistic regression analysis was improved brain perfusion 2 hours after treatment,

assessed as a decrease of >30% in the volume of hypoperfusion on MTT maps. This criterion of early reperfusion was a stronger predictor of clinical outcome than patient age or baseline clinical severity measured by the NIHSS, 2 clinical variables that are highly predictive of outcome. Thus, with the administration of a clinically effective thrombolytic therapy, early reperfusion by MRP predicted clinical recovery.

This use of perfusion with diffusion MR as a selection variable and as a surrogate outcome measure was applied in the DIAS phase II trial.[8] It was the first prospective, randomized, placebo-controlled thrombolytic stroke trial to use MRI both to determine patient eligibility and as a primary efficacy end point. A diffusion/perfusion mismatch by visual inspection was an inclusion criterion for this trial, which involved 104 patients within 3 to 9 hours of symptom onset. A primary efficacy end point was the rate of reperfusion on MRI after 4 to 8 hours, defined as either ≥30% reduction of MTT lesion volume or ≥2 points of improvement on the adapted Thrombolysis In Myocardial Infarction (TIMI) grading scheme with MRA. This trial demonstrated that intravenous desmoteplase was associated with a higher rate of early reperfusion and better 90-day clinical outcome in the patients selected for treatment than in the placebo group.

Summary

Although widely accepted and used in practice, the diagnostic and clinical utility of perfusion MRI has not been proven in controlled, adequately powered studies. Descriptive case series and studies of the relationship of MRP parameters to other clinical, imaging, and therapeutic variables have shaped the concepts and hypotheses about its potential utility (LOE: B, C). The identification and response to treatment of the ischemic penumbra pattern when defined as a simple diffusion/perfusion mismatch may be the most useful application of perfusion MR, both for patient selection and as an outcome measure in clinical trials. Individual centers have demonstrated that different MRP parameters are generally predictive of tissue fate and clinical outcome; however, despite these different methods already being applied, 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, final infarct size, and clinical outcome on which the measures of accuracy are based. Furthermore, time to reperfusion affects these parameters and is an integral component in the evaluation of all MRP methods, yet it often is not taken into account. To progress toward a consensus on the optimal perfusion MR technique to use in the diagnosis and management of acute ischemic stroke, it is imperative that multicenter, prospective, systematic trials be conducted to fully evaluate this promising tool.

Summary of Perfusion Imaging Techniques

1. SPECT: In terms of making decisions as to whether to perform thrombolysis, and in terms of patient outcome, perfusion from collaterals to the ischemic region may be as important a variable as time from ictus (LOE: A).
2. XeCT: Quantification appears to be important in predicting patient outcome. CBF thresholds and volume of infarction determined by these thresholds correlate with outcome (LOE: B).
3. Although CTP is more easily quantified than MRP, the accuracy of that quantitation is still being debated (LOE: B).
4. Normalized quantitative thresholds as determined by CTP, which differentiate potentially viable and nonviable ischemia within the penumbra, are similar to the relative threshold values found with SPECT (LOE: B).
5. The core of initial infarction is determined similarly with DWI, CTP-CBV, CTA-SI, and XeCT CBF <12 mL · 100 $g^{-1} \cdot min^{-1}$ (LOE: B).
6. With successful recanalization, outcome strongly correlates with the volume of the initial core of infarction. The threshold of 100 mL, as found in CTP studies, is approximately one third of the MCA territory, as found in older tPA clinical studies. Patients with infarctions equal to or greater than that size tend to have poor outcomes (LOE: A).
7. A combination of values derived from dynamic CT studies, reflecting size of initial core and volume of salvageable tissue, may predict clinical outcome with successful recanalization better than clinical parameters (eg, NIHSS) alone (LOE: B).
8. MRP is difficult to quantify because of a lack of a linear relationship between contrast agent concentration and signal intensity (LOE: B).
9. There are a variety of MRP maps; which one best predicts tissue fate and clinical outcome is still being debated (LOE: B).
10. A combination of MRA, DWI, and multiple MRP parametric maps can be used operationally to select patients for acute therapy (intravenous versus intra-arterial thrombolysis versus mechanical thrombectomy versus conservative management; LOE: B).
11. Diffusion/perfusion mismatch (the specific perfusion map in debate) may be used to select the appropriate patient for thrombolysis, especially within the patient group that is >3 hours after ictus (LOE: B).
12. Changes in MRP (specific map still in debate) may serve both as a surrogate marker of treatment efficacy and a predictor of clinical outcome. Changes in dynamic CTP data may serve the same functions (LOE: B).

Recommendations

Perfusion-Derived Values

Quantitative thresholds of tissue that is dead or destined to die versus tissue that is still living and may be salvageable are the goal of all perfusion techniques. Although the performance of such studies may be considered to identify and differentiate the ischemic penumbra and infarct core, their accuracy and usefulness have not been well established (Class IIb, LOE: B).

Clinical Role of Perfusion Imaging

1. The admission volumes of infarct core and ischemic penumbra may be significant predictors of clinical outcome, possibly exceeding the prognostic value of admission NIHSS score (Class IIb, LOE: B).
2. There is increasing but as yet indirect evidence that even relatively imprecise measures of core/penumbra mismatch may be used to select patients for treatment beyond a strict 3-hour time window for intravenous thrombolysis. Together with vascular imaging, these approaches may determine suitability for other therapies such as mechanical clot retrieval and intra-arterial thrombolysis, as well as provide a surrogate marker for treatment efficacy (Class IIb, LOE: B).

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*Modest.

†Deceased.

‡Significant.

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Stroke
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Recommendations for Imaging of Acute Ischemic Stroke: A Scientific Statement From the American Heart Association

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on behalf of the American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, and the Interdisciplinary Council on Peripheral Vascular Disease

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