CT, MR Imaging, and MR Angiography in the Evaluation of Patients with Acute Stroke

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The patient with acute stroke presents a full challenge to the diagnostic and therapeutic aspects of medicine in all forms, from community through tertiary care. Patients with brain damage in the ischemic, but not yet infarcted, phase have the greatest potential for recovery. Herein, the author reviews the most commonly employed diagnostic tools that are currently used before stroke therapy. The logistical demands of emergency evaluation of a patient at a given institution often dictate which modality can and should be practically applied. Any of the available modalities, when used well, can offer pertinent diagnostic and even predictive information to assist in the quick, accurate classification of patients to the most appropriate treatment group.

THE symptoms of stroke remain myriad but center on common loss of the neurologic functions of movement, sensation, expression, cognition, and consciousness. Therefore, stroke or cerebral infarction should be suspected in any patient who may present with paresis, paralysis, dysphasia, confusion, drowsiness, or even coma. In its earliest phases, this disorder will typically represent acute cerebral ischemia before the path toward infarction. For those with a greater tendency to intervene, patients with brain damage in the ischemic, but not yet infarcted, phase represent the target of greatest potential recovery. As with all medicine, the best treatment depends on the earliest, clearest, and, at times, fastest path to correct diagnosis. Many options are available for patients with symptoms typical of acute stroke.

COMPUTED TOMOGRAPHY (CT)

CT is the most common modality offered in the average hospital in the United States. Thus, conventional unenhanced head CT is the typical screening tool used for a patient presenting with acute neurologic symptoms of stroke.

First and foremost, head CT will quickly enable the diagnostician to ascertain whether the acute situation involves any form or degree of intracerebral hemorrhage. Should the CT scan be positive for hemorrhage, then the subtype will lead to differing differential categories. In review from outer toward inner, epidural and subdural hematomas most typically result from trauma. The latter will also commonly occur in times of coagulopathy and, in the elder patient, may often occur idiomatically. The classic subarachnoid hemorrhage will typically represent either trauma or ruptured intracerebral aneurysm. In the absence of a substantial history of trauma, the presence of acute subarachnoid hemorrhage naturally leads to a diagnostic evaluation to find the likely aneurysm. A parenchymal hematoma often occurs in the basal ganglia, thalami, or posterior fossa as a result of hypertension (1). Other possible sources may include vascular malformations, tumors, mycotic aneurysms, or other vasculopathies. Depending on the size and source of the hematoma, some therapeutic interventions are possible. In particular, the placement of a drainage catheter, at times with administration of a fibrinolytic agent, may reduce the morbidity by reducing mass effect (2).

In the absence of hemorrhage, the physician must search for signs of acute nonhemorrhagic cerebral ischemia. The sensitivity of unenhanced head CT for this disorder increases with the size of the ischemic territory and the length of time from the onset of the ischemic insult. Subtle early signs of ischemia center on identifying a loss of the so-called gray-white differentiation; this represents the distinction in attenuation readings between the thin cortical and deep central areas of neuronal gray matter from the thicker underlying yet less dense areas of white matter axonal tracts (3). In ischemia, that involves the middle cerebral artery (MCA) territory. This loss will first manifest along the insular cortex as the so-called lost definition of the insular ribbon (4). This same principle can be applied anywhere along the gray-white matter borders, and careful scrutiny will improve identification. Certain helpful techniques include review of all borders of the basal ganglia.
and comparison across the midline for additional changes of early sulcal effacement. When reading in a softcopy mode, a change of window and center levels may increase the conspicuity of these changes (5). Careful review along the base of the brain will at times reveal increased attenuation within the MCA itself, the so-called dense MCA sign (6). Unfortunately, such a sign is also suggestive of a poorer prognosis. When areas of lost parenchymal differentiation are accompanied by edema and mass effect of approximately more than one third of an MCA territory, then prognosis also worsens (7). Thus, even the most commonly available tool, unenhanced head CT, can help the physician distinguish among the types of stroke and start patient stratification for therapy choices.

CT Angiography

The current development and deployment of multisection CT technology has advanced the diagnostic potential of this modality. First, these machines enable the high-speed acquisition and processing necessary to produce quality angiographic projections of both the cervical and cerebral vasculature. In the setting of acute subarachnoid hemorrhage at unenhanced head CT, the standard today still requires conventional catheter angiography; however, the debate has begun regarding the potential for replacement by CT angiography (8).

Naturally, this technique has also been used to evaluate patients who present with acute symptoms of stroke but do not have hemorrhage. In a study of patients with hyperacute stroke, Lev et al (9) showed that the examination and necessary processing could be completed within an average of 15 minutes. They further demonstrated that the sensitivity and specificity of CT angiography in the detection of large-vessel occlusions are higher than those of catheter angiography. Verro et al (10), however, found that two of 14 lesions seen on CT angiograms could not be found on subsequently obtained catheter angiograms. Similarly, in a different series of patients who underwent CT angiography after the onset of acute stroke symptoms, a subset of seven patients with a positive CT examination subsequently underwent catheter angiography. In one of these seven patients, the catheter examination failed to demonstrate any correlative lesion (11). These represent potentially disturbing false-positive CT findings or interval autolytic correction of the occluding embolus. Further testing of the limits of such CT examinations in very acute settings will ultimately help distinguish the sensitivity and, thus, the reliability. Nevertheless, the results of these studies do, in general, support the accuracy of CT angiography in the identification of large-vessel occlusive disease.

Viewed from the opposite perspective, the above data argue that if sufficient diagnostic accuracy can be obtained, CT angiography may serve as a sufficient screening technique for excluding large-vessel thromboembolic disease as a cause for a patient’s current symptoms (Fig 1). Such information would contribute to the fast and accurate categorization among the potential subtypes of stroke. Indeed, Wildermuth et al (11) found that the use of CT angiography to screen for nonhemorrhagic acute stroke can help select those patients in whom autolysis of clot may already have occurred and, therefore, in whom the administration of thrombolytics would be unnecessary. Further, they suggested that CT angiography may help select poor candidates for acute thrombolytic therapy from even those whose examinations are positive for large-vessel occlusions. This exclusion process, they believe, may even occur among those patients in whom the CT angiogram has shown a large-vessel occlusion (eg, those with occlusion of the internal carotid artery at the level of the cerebral bifurcation or those with poor collateral supply that might have sustained tissue until restoration of the primary flow) (11).

The sensitivity of CT angiography has been evaluated in several anatomic compartments. In the cervical carotid bifurcation, CT data have been compared with those obtained with ultrasound and, again, digital subtraction catheter angiography. Overall, most investigators have found a good correlation with digital subtraction angiography. Further distinction occurred when comparing specific degrees of stenoses among the positive examinations. Under this scrutiny, the
source images, rather than the maximum intensity projections or shaded-surface displays, proved most accurate; however, even a review of source images could not enable the accurate differentiation of moderate from severe stenoses (12).

The strong effects of bone density on CT scans can confound the processing needed to produce clear angiographic projections for clinical interpretation. In a series of patients who presented with acute stroke symptoms from the posterior fossa, Graf et al (13) studied 22 patients with posterior cerebral circulation by using both CT and catheter angiography. There was better correlation between the two modalities when the lesion was in the basilar artery. For vertebral lesions, although the CT studies depicted a problem, the identification of a specific lesion type occurred in only half the cases.

CT Perfusion

The modern multissection CT unit may also be used to generate CT perfusion data. In a study that included patients without stroke, patients with old stroke, and patients with hyperacute stroke, Hunter et al (14) were able to demonstrate the sensitivity of perfused cerebral blood volume maps for detecting the changes in hyperacute stroke. CT perfusion parameter maps were generated when density curves came from repeat images obtained during bolus administration of contrast material. This technique has been developed and used for several years with various perfusion analyses. Postprocessing relies on mathematical deconvolution of the time-density curves to enable the calculation of relative cerebral blood flows, cerebral blood volumes, and mean transient times for every anatomic location. The major limitation of the technique, however, remains the need to image one, two, or four continuous sections of the head, depending on the capacity of the multissection scanner. This necessitates repeat imaging at 1 to 2-second intervals for approximately 1 minute. There is, therefore, also concern for radiation exposure if the orbits are included. Nevertheless, Eastwood et al (15), in a comparative analysis of 12 patients with acute MCA stroke and 12 control subjects, demonstrated a significant decrease in cerebral blood flow and cerebral blood volumes in affected patients. Not surprisingly, the results of that study also confirmed a significant increase in the mean transient time in the affected distributions.

CT perfusion calculated by tracking a bolus of iodinated contrast material has been studied for reproducibility and accuracy. In a study of patients with tumor (16), CT perfusion data were collected in the same patients within 24 hours. The authors reported a strong correlation coefficient in the perfusion parameters when data were collected at different times but over the same regions of interest; a correlation coefficient of 0.88 was reported. In an attempt to demonstrate accuracy, the quantitative perfusion calculated from CT based on tracking and processing of a bolus of iodinated contrast material was compared with perfusion parameters obtained from xenon gas-enhanced CT. Historically, xenon gas CT has been shown to correlate reasonably well with microsphere perfusion in primate animal models. In this more current comparison with iodinated CT perfusion, correlation coefficients of approximately 0.75 were obtained for cerebral blood flows generated with the two techniques (17). Additional comparisons with calculated relative cerebral blood volume from iodinated perfusion CT were made with cerebral vascular reserve from the xenon studies, and these showed a strong negative correlation. Again, not surprisingly, regions of delayed time to peak on iodinated CT parameter maps corresponded with areas of decreased blood flow on xenon CT maps. In general, the time-to-peak regions were larger in volume, and this does correlate with magnetic resonance (MR) imaging data about time to peak, which also suggest an increased volume relative to final infarct in the same territories.

It is now increasingly clear that with increased access to a modern multissection CT scanner, at least reasonable initial classification of a patient with acute stroke may be performed. Unenhanced head CT may be used to exclude hemorrhagic stroke. Then, a large-field-of-view CT angiogram may be obtained after the administration of approximately 50 mL of contrast material to evaluate for large-vessel occlusion. Finally, with the addition of approximately another 50 mL of contrast material, a window of cerebral perfusion can be examined for a slab thickness of up to 2 cm with current machinery (Fig 2). A combined scoring method has been offered that includes all three components from these examinations, and it is not surprising that the component score better represents the prognosis of the tissue at risk (18). The cost of these examinations in terms of stroke classification must be measured in time expended. It has been estimated that such a CT examination can be performed in approximately 20 minutes, including postprocessing time, with a modern scanner and well-trained technologists. We must remember that this is a performance statement based on maximum limits of machine and personnel function. Nevertheless, this is the standard that has been set by MR imaging and does allow for better stratification of outcome as well as selection of therapy.

MR IMAGING

MR examinations usually provide better conspicuity and offer improved visualization of the changing physiology of brain tissue in stroke settings. This arises naturally from the improved depiction of soft-tissue changes and the exquisite sensitivity of water in human tissues to changes in the surrounding cellular environment. Even routine MR imaging with conventional spin-echo techniques enables improved displays of the ischemic brain relative to CT (19). The application of such conventional sequences best demonstrates the early edematous changes in the interstitial spaces that produce cortical swelling and gyral thickening with the adjacent effacement of sulci (20). The vasogenic edema is best detected with T2-weighted or fluid-attenuated inversion-recovery (FLAIR) sequences, and the changes of cortex and sulci are often better seen with T1 weighting. However, comparison of even these two data sets begins to allow temporal distinction in the times from initiation of the ischemic event. The morphologic changes seen with T1 weighting are particularly apparent 1 day after the event, and they diminish within 3 days from onset. The increased signal intensity on the T2-weighted images,
in comparison, appears earlier, usually within 8 to 12 hours from onset, as the effects of increasing cellular free water appear after the adenosine triphosphate–dependent pumps have fully failed. The added advantage of FLAIR imaging resides in the relative suppression of signal from free cerebrospinal fluid (Fig 3). This, in turn, renders any abnormal signal in the parenchyma, even if adjacent to the cerebrospinal fluid spaces, to appear completely conspicuous (21).

MR Diffusion

The development and application of diffusion-weighted images and parameter maps has dramatically changed our ability to evaluate the most acute changes of cerebral ischemia in patients with stroke. Diffusion images as originally conceived are generated from gradients applied in multiple directions and at different strengths to enable the calculation of trace images and diffusion coefficient maps (22). The former permits assessment of true diffusion abnormalities on the images, rather than areas of increased signal intensity that occur secondary to the anisotropic organization of the tissue, principally because of the tracks of myelinated white matter. The quantitative coefficient maps, or apparent diffusion coefficient (ADC) maps (ADC of water), enable the distinction of increased signal intensity on diffusion that arises from true diffusion restriction from that which occurs because of an overwhelming contribution from T2-weighted signal. This occurs as so-called “T2 shine-through” and most often represents the effects of associated and later-arriving vasogenic edema. Early studies of animal models demonstrated changes on diffusion images even within the first 30 minutes from onset of ischemia (23). These are postulated to represent some effect similar to cytotoxic edema, in which water becomes trapped at a molecular level, if not in the cells, than along the disrupting cell membrane amid the changing macromolecular environment along the cell surface. On diffusion-weighted images, these appear as areas of high signal intensity, and on corresponding ADC parameter maps these appear as regions of decreased diffusion that are mapped to the dark gray or black tones (Fig 4). In humans, these examinations can be obtained over the whole head in as little as 3 seconds, and a total diffusion analysis can be performed in less than 1 minute.

The addition of diffusion-weighted MR imaging to the evaluation of patients with acute stroke has changed vividly the sensitivity for detecting the early signs of cerebral infarct. Early on, these techniques showed sensitivity for changes of human cerebral infarct, even within 3 hours of ischemic stroke onset (24); sometimes, such changes have been seen within 45 minutes. More recently, Kidwell et al (25), in a study of patients in whom transient ischemic attacks were diagnosed on the basis of clinical criteria, found diffusion abnormalities in almost half of them. In a large series of 691 patients who presented less than 6 hours from symptom onset, Mullins et al (26) reported that diffusion-weighted imaging had a sensitivity of 97% and a specificity of 100%. The sensitivities of conventional MR imaging and unenhanced head CT are 60% and 40%, respectively. The comparative specificities are 100% and 92%, respectively. Evaluation of stroke patients with conventional unenhanced head CT alone should be considered insufficient. The addition of at least MR diffusion or CT perfusion is necessary for adequate evaluation.
Analyses of the quantitative diffusion images—the ADC maps—may reveal more information regarding the reversibility of the damaged brain tissues. In the first 4 days following a stroke, the diffusion within infarcting tissue will remain restricted. The diffusion will pass through normal ranges (pseudonormalization) beginning at 7 days (Fig 5) and end with unrestricted diffusion of free water in cerebrospinal fluid during the next several weeks (27). Further study of regions of abnormal diffusion has demonstrated a more heterogeneous pattern of restriction than originally anticipated. This suggests that all areas of central infarction are not equal, and that, at the least, one can expect differing temporal patterns of progression in the evolution of diffusion changes (28).

Importantly, physiologic variations in the effect of diminished ADC values have been reported. In a series of almost 50 patients with abnormal diffusion maps and at least 1-month follow-up, Grant et al (31) reported no reversal of ADC lesions. Yet the same authors also reported that they found five individual cases that did reverse. They estimated their observed incidence of ADC reversal in natural history at less than 1%. However, these patients did not undergo any intervention in an attempt to salvage tissue. In a different study, Fiehler et al (32) reviewed diffusion maps and data from MR angiography. They identified a significant reduction in lesion volumes in four of 15 (27%) patients. They were also able to correlate these reductions with those patients who demonstrated recanalization of vessel occlusions on the MR angiograms. Overall, these data suggest that diffusion lesions, in the absence of restoration of flow and perfusion, will result in permanent tissue infarction. They also suggest that active intervention or natural recanalization that restores flow can produce salvage—that is, some areas of decreased diffusion represent regions of damaged tissue that may still accept rescue. Thus, at best, diffusion changes reflect an estimate of core infarct tissue and are not a guarantee of cellular death.

**MR Perfusion**

MR examinations may also be used to generate perfusion maps by processing hemodynamically weighted image sets. Typically, a high-speed echo-planar sequence can be applied with T2* weighting over the whole brain (rather than a 2-cm slab as in the iodinated CT studies described earlier). This can be readily repeated every 1 to 2 seconds to establish a baseline equilibrium image set and then to follow the arrival, peak effect, and washout phases of a bolus of gadolinium (33). These sequences are specifically designed for their sensitivity to magnetic metal susceptibility effects (34). Rather than having sensitivity to susceptibility produce an artifact as the gadolinium passes through, it can be used to track the diminishing signal intensity and then the asymptomatic return toward baseline at every pixel. In turn, a graph of signal intensity changes over time is created at each pixel point. This curve can then be further processed to produce the typical parameter maps that have been discussed for CT: time-to-peak effect, relative cerebral blood flow, relative cerebral blood volume, and mean transit time.

The various MR perfusion parameter maps have allowed many investigators to better distinguish the location, extent, and type of ischemia from which a given patient with stroke may be suffering. Tissues distal to arterial occlusion appear with a decrease in

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**Figure 3.** Typical FLAIR axial MR image reveals the usual high signal intensity seen with an acute nonhemorrhagic infarct in the right MCA territory. Note the ready conspicuity of the abnormality against the suppressed cerebrospinal fluid background.

**Figure 4.** (a) Axial diffusion-weighted MR image clearly shows an increase in signal intensity in the right MCA distribution. This is consistent with hyperacute, acute, or even early subacute infarct without concurrent hemorrhage. (b) Map contains the concomitant ADC map that presents the expected darker tones in the affected area that visually represent the quantitatively low-diffusion coefficients.
the relative cerebral blood volume (35). Further applications have shown an ability to distinguish the degree and capacity of natural collateral supply beyond a known arterial occlusion in the human brain. In the study by Reith et al (36), good collateral supply appeared in conjunction with only a slight increase in mean transit time or relative cerebral blood volume, whereas patients with poor collateral vessels demonstrated a more statistically significant increase.

The analysis of diffusion and perfusion data combined permits the unique estimation of tissue under ischemic stress at risk for infarction. An estimation of such ischemic penumbra represents a contribution afforded to the physician with modern MR imaging in acute stroke in comparison to all other imaging modalities. Initially, Sorensen et al (37) reported on the specificity of simultaneous and superimposed abnormalities on diffusion images and perfusion maps in accurately predicting those tissues that would infarct, even in the setting of otherwise normal findings at head CT and conventional MR imaging. Physicians then began to anticipate that this information might have accurate predictive value with regard to patient outcome (38).

By using the area of abnormal diffusion signal as an estimate of core infarct, the additional areas of hypoperfusion serve as a working estimate of the remaining tissue at risk, the penumbra (Fig 6). In a comparison of diffusion data with multiple perfusion parameters, Sorensen et al (39) reported that regions of decreased relative cerebral blood flow that exceeded the area of diffusion abnormality enabled the prediction of infarct growth. They further noted that any abnormal area exceeding the diffusion changes on relative cerebral blood volume maps did not enable the prediction of growth. Predictive data that described the ischemic penumbra for a given patient with acute stroke enabled improved classification of patients for appropriate therapy when the time to peak perfusion parameter map was compared with the diffusion changes to estimate penumbra (40).

Further analyses have allowed us to show that the addition of perfusion data remains crucial for correctly assessing a patient in the hyperacute stroke period (the initial 6 h from symptom onset). Diffusion data alone can be very sensitive in the first 24 hours from onset (41) or even in the first 6 hours (42). However, the perfusion data can be required in one-fourth of all patients to correctly detect the true ischemic lesions that may pre-

Figure 5. (a) T2-weighted MR image demonstrates an area of abnormal high signal intensity in the right posterior cerebellar hemispheres, a finding that is consistent with an infarct that is at least 8–12 hours old (but may be several weeks old). The absence of mass effect suggests that the infarct did not occur in the period of maximum edema from 1 to 3 days from onset. (b) MR image obtained in the same section position used in a. Note the lack of observable distinction between the normal and affected hemispheres. This represents the “pseudonormalization” of diffusion signal that typically occurs in the 1–3 week, early subacute time frame.

Figure 6. (a) Axial diffusion-weighted MR image is somewhat distorted by artifact but does not reveal any distinct area of abnormal signal intensity. This suggests that this patient, although having symptoms of acute stroke, may be free of ischemic disease. (b) Time to peak perfusion parameter map, however, shows that this patient has substantial ischemia in the territory of the anterior division of the left MCA. Had the imaging work-up of this individual been limited to diffusion-weighted imaging, the defect and the opportunity to intervene and correct the problem would have been lost.
cede infarction and, therefore, represent the most salvageable tissues (43). This may be especially relevant and more frequent in the first few hours from symptom onset.

MR perfusion may also help determine patient prognosis. Fiehler et al (32) examined diffusion and MR perfusion parameters acquired before and after treatment with systemic thrombolytic drugs. They found that combined thresholds of less than 12 mL per 100 g per minute of flow and more than 50 mL of abnormal tissue volume served as accurate predictors of infarct growth and worse patient prognosis (32). Similarly, a combined view of quantitative data from both diffusion ADC and perfusion relative cerebral blood flow maps allows distinction of potentially viable tissue amenable to intervention from those patients or regions that unfortunately have no residual chance of rescue (44). Specifically in areas of perfusion diffusion mismatch, regions beneath thresholds of relative flow or blood volume were predictive of progression to infarct (45). Nevertheless, these maps can cause overestimation of the amount of tissue that will infarct if untreated. The mean transit time and similar time-to-peak maps tend to do this to a greater degree than do other parameters (46).

**MR Angiography**

MR imaging data can be combined with MR angiographic data to more directly evaluate vessel anatomy and patency. Traditional MR angiography consists of bright blood images generated and then processed into maximum intensity projections (47). These are reliable methods to display the skull base, cervical, and intracranial arterial anatomy. Common limitations occur from skull base and paranasal sinus susceptibility affects, from vessel tortuosity that affects direction or phase, and from common patient motion issues. MR angiograms derived from a patient with acute stroke symptoms may help confirm the presence of an acute arterial dissection as the underlying cause of the ischemia (48).

As for CT, the current state of the art in MR angiography centers on timed imaging of contrast-enhanced vessels caught in the correct phase of the bolus transit. A single acquisition can display all the anatomy, from the aortic arch, through the cervical carotid bifurcations, through the circle of Willis at the base of brain, and into the proximal cerebral branches (Fig 7) (49). Limitations of tortuosity and susceptibility remain but are contained to the focal regions of maximum interference.

In summary, there are many choices available for the imaging evaluation of patients with acute stroke. Each has its own advantages and disadvantages. In general, the logistical demands of emergency evaluation often dictate which modality can and should be practically applied. Thus, any of the available modalities, when used well, can offer helpful, pertinent, diagnostic and even predictive information to assist in high-speed, accurate patient classification. This will help improve the outcome from the dramatic damage caused by acute cerebral stroke.

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Figure 7. MR angiogram projection shows the tremendous field of view attainable with use of a bolus of gadolinium. The arch, carotid bifurcations, skull base vessels, and circle of Willis are clearly depicted. Similar large-field-of-view angiographic representations can be obtained with multisection CT and excellent postprocessing techniques.
References


