

Fundamental and Advanced Imaging Techniques in the Treatment of Acute Stroke Patients

Introduction

The main goals of imaging in ischemic stroke have been to establish the diagnosis of ischemic stroke and to exclude a nonischemic or hemorrhagic cause of the patient's presentation, eg, brain tumor, intraparenchymal hemorrhage, subarachnoid hemorrhage.¹

Recently, imaging of ischemic stroke has been revolutionized by developments in imaging modalities which enable more rapid and accurate identification of acute cerebral infarction. During the same period, multiple clinical trials of intravenous and intra-arterial thrombolysis, as well as mechanical clot removal in the treatment of ischemic stroke, have shown that success of interventions depends on the timely and accurate imaging detection of acute stroke to identify the patients who meet the inclusion criteria of therapy. Advances in the imaging of acute stroke have the potential to aid in the improved selection of patients in whom the benefits of therapeutic interventions outweigh its potential risks. Advances in stroke imaging techniques allow a more accurate detection of an acute stroke, assessment of the state of intracranial circulation, parenchymal perfusion, and volume of potentially salvageable brain parenchyma.²

In order to understand the benefit of imaging techniques utilized in the diagnosis and therapy of ischemic stroke, it is necessary to comprehend the pathophysiology of ischemic stroke and the subsequent gross pathologic changes in brain parenchyma that are reflected in imaging.

Pathophysiology of Ischemic Stroke and Evolution of Parenchymal Damage

The characteristic imaging findings of ischemic stroke may best be understood in the context of the evolution of injury to the brain parenchyma. Ischemic stroke is caused by a thrombotic or embolic occlusion of an

intracranial blood vessel, which results in diminished or absent blood flow to the area of brain parenchyma that it supplies.^{3,4}

Ischemic injury of brain parenchyma is a result of energy depletion, due to the decrease in cellular oxygen and glucose, which leads to a cascade of events ultimately leading to cell death. The loss of stored cellular energy leads to the shutdown of ATP-dependent cell membrane ion pumps, resulting in the loss of ionic gradients, leading to intracellular ionic imbalance. Cellular excitotoxicity occurs as a result of release, diminished reuptake and excessive stimulation by neurotransmitters such as glutamate, which binds to and activates NMDA and AMPA receptors. Ischemia and reperfusion cause oxidative and nitrosative stress to neurons, due to the adverse actions of reactive oxygen and nitrogen radicals. The most significant mechanism of neuronal death in ischemic stroke is the apoptotic cascade, which causes the loss of integrity of neuronal membranes and the failure of organelles. Subsequent inflammation of the wall of blood vessels and brain parenchyma propagates tissue damage.⁵⁻⁷

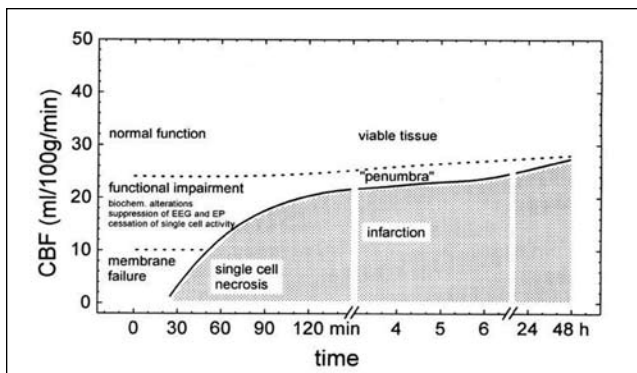
The combined effects of cytotoxic and vasogenic edema cause swelling and mass effect on adjacent brain parenchyma. Within minutes of the ischemic event, an ionic imbalance develops within neurons, leading to the intracellular accumulation of sodium. Cytotoxic edema occurs as a result of water entering the cell in order to maintain osmotic equilibrium. Within the first days to weeks after infarction, the cytotoxic edema increases, and resolves within one month. Within hours to days of the infarction, vascular injury caused by the ischemic stroke creates an increase in permeability of brain capillaries, leading to extravasation of serum proteins and plasma into adjacent parenchyma, or vasogenic edema. In the chronic stage after infarction (>3 months), volume loss and gliosis of the affected gray and white matter

occurs, accompanied by parenchymal atrophy and Wallerian degeneration and rarely, calcification.⁸⁻¹⁰

In the setting of acute ischemic stroke, the extent of parenchymal injury is dependent on the relative decrease in cerebral blood flow (rCBF). Normal cerebral blood flow in the adult brain is estimated to be between 45–65 mL/100 g/min, with baseline cerebral blood flow in gray matter in the range of 60–70 ml/100 g/min, which is significantly greater than CBF in white matter, at 20 ml/100 g/min.^{5,11-13}

Hypoperfusion indicates values below this level. When rCBF drops below approximately 25–30 ml/100 g/min, neurologic impairment is observed. The electrical failure of brain parenchyma occurs between 16–20 ml/100 g/min, and cytotoxic edema is observed at 10–12 ml/100 g/min. At rCBF levels below 10 ml/100 g/min, metabolic failure of tissue is observed.^{11,12,14}

Figure 1. Flow thresholds for preservation of function and morphology of brain tissue. (Source: Heiss WD, Graf R, Grond M and Rudolf J. Quantification of Neuroimaging for the Evaluation of the Effect of Stroke Treatment. *Cerebrovasc Dis* 1998;8(suppl 2):23–29).



Hypoperfused tissue may be divided into several principal compartments, based on the likelihood of survival. At CBF levels below 18 – 20 ml/100 g/min, ischemia places the tissue at risk for irreversible damage unless blood flow is restored. When CBF is between 10 and 20 ml/100 g/min, cell death may occur between minutes to hours, and when CBF falls below 10 mL/100 g/min, infarction occurs within minutes. The core of the infarction represents tissue which has been irreversibly damaged due to insufficient blood supply.^{1,12,13}

The ischemic penumbra is tissue that has impaired function but preserved integrity due to the reduction of blood flow to less than the penumbral threshold but greater than the threshold of infarction. The ischemic penumbra is further defined by abnormal neural function which may be correlated with clinical

symptoms, possessing characteristics of cellular dysfunction but not death, as well as having an uncertain fate. The basis of current therapy for acute stroke is the salvage of the ischemic penumbra by restoring blood flow, which has been shown to improve clinical outcomes.^{12,15}

Computed Tomography (CT) Findings in Ischemic Stroke

In the acute imaging of ischemic stroke, there are several roles for CT imaging. Noncontrast CT can differentiate ischemic stroke from hemorrhagic stroke in the acute clinical setting, which has a significant implication on therapy.¹⁶ The identification of a significant hemorrhage in acute stroke is crucial, since this is a contraindication to thrombolytic therapy. The location and extent of brain parenchyma and vasculature affected by ischemic stroke may also be identified by CT.

The CT findings in ischemic stroke vary by the amount of time post-ictus. Contrary to the accepted notion that hyperacute infarction has no signs on plain CT until four to six hours after infarction, abnormalities may be seen in 75% of patients with a large middle cerebral artery (MCA) stroke within three hours of stroke onset.^{1,16,17}

One of the early signs of ischemic stroke on CT is hyperattenuation of the occluded artery. For example, an occlusion of the proximal MCA may be seen as high density within the vessel due to a thrombus or a calcified embolus which inhibits blood flow to distal MCA segments. The hyperdense MCA (HMCA) sign may be confirmed by comparing the density of the infarcted proximal MCA with the contralateral MCA to verify that it is in fact asymmetrically hyperdense.^{1,16}

Figure 2. The arrow points to a hyperdense M1 segment of the left middle cerebral artery (MCA) due to an intraluminal thrombus, causing an acute infarction in the distribution of the left MCA.



Within six hours of infarction, cytotoxic edema of affected brain parenchyma can cause a loss of definition of the border between gray and white matter, leading to several findings.^{1,18} In infarctions involving the MCA, the loss of clear definition in the junction between gray and white matter in the lateral insula is known as the loss of the insular ribbon (insular ribbon sign). The lentiform nucleus may also be obscured due to hypodensity of the surrounding area. Brain edema, causing localized mass effect will result in sulcal effacement and unilateral ventricular compression.

Figure 3. Acute large left MCA distribution infarction with brain edema with effacement of sulci within the left cerebral hemisphere with mass effect on the left lateral ventricle causing effacement and a subfalcine herniation to the right.



Mass effect increases until three to five days after the ictus, and after four weeks, mass effect resolves and the lesion is characterized by chronic hypodensity due to the loss of parenchyma.^{1,16}

Within 24 hours of an ischemic event, an indistinct area of low density develops in the distribution of occluded vessel. Between the second and third weeks after the infarction the CT fogging effect may occur, which denotes the change from low density to isodensity in the distribution of the infarcted vessel in 20–40% of large infarctions. This change in density is thought to occur due to the influx of macrophages, capillary proliferation, hemorrhagic transformation of the lesion and net decrease in water in the lesion. After four weeks, the infarcted area reverts back to a low density area. Persistent hyperdensity may occur in the cortex if laminar necrosis has taken place, leading to deposition of compounds such as heavy metals or calcium.^{1,19,20}

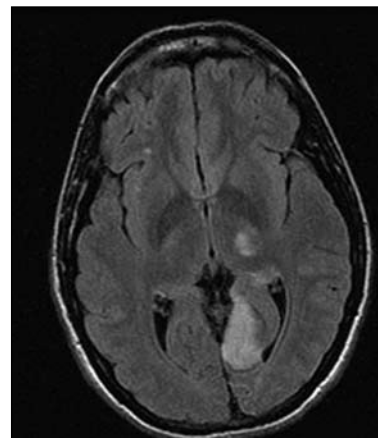
Contrast enhancement of the lesion may be observed if the blood-brain barrier has been disrupted by the infarction, and if the contrast is able to reach

the ischemic area. If enhancement is seen within 24 hours, the embolus has moved distal to the area of occlusion, or the embolus is affecting an area with good collateral circulation. Between the second and third weeks post infarction, enhancement may be seen in 70% of lesions. The shape of the area of enhancement is typically gyriform if the ischemic area involves the cortex, or ring-shaped if it involves deeper structures such as the brain stem or basal ganglia. The CT enhancement of infarction may last for several weeks, typically resolving after four weeks.¹

Magnetic Resonance Imaging (MRI) Findings in Ischemic Stroke

Magnetic Resonance has been shown to be as sensitive as CT to rule out acute parenchymal hemorrhage in the imaging of acute stroke. The MRI findings in ischemic stroke depend on the size and location of the infarction, and most significantly, on time from the ictus. Acute findings are seen on T1-weighted, T2-weighted, and T2 FLAIR imaging within the first 6 to 12 hours, and typically develop within the first 24 hours of the ischemic event.^{9,21}

Figure 4. T2 FLAIR weighted axial image showing acute left PCA distribution infarctions with involvement of the left thalamus, left paramedian occipital lobe and left posterior temporal lobe.



Immediately after a stroke, the occlusion of an intracranial vessel may be seen as T2 FLAIR hyperintensity from within the vessel. The absence of flow results in the loss of the normal flow void which is normally seen with flowing blood.^{1,9,16}

Gross morphologic changes of brain parenchyma may precede signal changes of areas affected by infarction. Within a few hours of the infarction, swelling of the cortex may be observed on T1 and FLAIR imaging. Within 12 hours of the infarction, edematous change is typically observed on T1WI in the

form of sulcal effacement, edema of gyri, and the loss of the interface differentiation between gray and white matter. Mass effect appears between 12 and 24 hours of the stroke, begins to resolve after 4 to 7 days, and is absent within 8 weeks. In the chronic stage (months to years), volume loss may be observed in the area of affected vascular distribution with compensatory enlargement of sulci, cisterns and ventricles.^{1,9,16}

Accompanying the gross changes in brain parenchyma are changes in signal intensity on T1 and T2 weighted imaging, depending on the elapsed time following infarction. Within eight hours, cytotoxic edema within the gray matter of the affected area is seen as hyperintensity on T2 weighted imaging.^{1,18} Within 16 hours, the lesion has low signal intensity on T1 weighted imaging. These T1 and T2 weighted imaging signal abnormalities are most prominent 1–2 days post infarction.¹⁶ The persistence of T2 hyperintensity is a chronic finding in ischemic stroke on MR imaging, due to gliosis and encephalomalacia that develop in affected areas of brain parenchyma.^{9,10}

However, within 1–8 weeks, the T2 fogging effect may be noted as the abnormal T2 signal hyperintensity partially resolves.¹⁶ The fogging effect is due to the same etiologies as seen in the CT fogging effect (influx of macrophages, capillary proliferation, hemorrhagic transformation of the lesion and net decrease in water in the lesion), and may lead to the underestimation of the size of the lesion in its chronic stage. The fogging effect may be avoided with the use of contrast enhancement to better visualize the lesion.^{19,20}

Immediately after large embolic occlusion, paramagnetic contrast enhancement may be observed within the vasculature adjacent to the lesion, most commonly observed in cortical lesions but also in lesions of the subcortical gray or white matter. The association of increased intravascular enhancement and better outcomes implies sufficient circulation to the lesion via leptomeningeal collaterals, which bridge ACA and MCA, PCA and MCA, superior cerebellar artery and PCA, and major cerebellar hemispheric arteries. Between 12 and 24 hours, contrast enhancement of the meninges adjacent to the infarcted area may be seen. Between one and three days post infarction, intravascular and meningeal enhancement begins to diminish, while contrast enhancement of the parenchyma starts to develop. Parenchymal contrast enhancement is most prominent between four to seven days post infarction, and may persist for up to eight weeks. As seen with contrast CT imaging, the amount of parenchymal contrast enhancement is correlated with the amount of collateral circulation supplying the lesion, as earlier and more intense enhancement may

be related to increased collateral blood supply.^{1,16,21-23}

Hemorrhagic transformation of tissue in ischemic stroke may be seen within one to three days due to the breakdown of the blood brain barrier, and is apparent in 25% of lesions by one week post-infarction. Hemorrhagic changes become chronic by eight weeks, when the hemorrhagic residua of hemosiderin and ferritin are seen as T1 and T2 hypointensity.^{9,16,24}

Magnetic Resonance Diffusion Weighted Imaging (DWI)

The development of diffusion weighted imaging (DWI) has revolutionized the imaging of acute ischemic stroke because it enables the accelerated identification of acute infarction and the ability to discriminate between acute and chronic lesions that result from infarction.^{9,25}

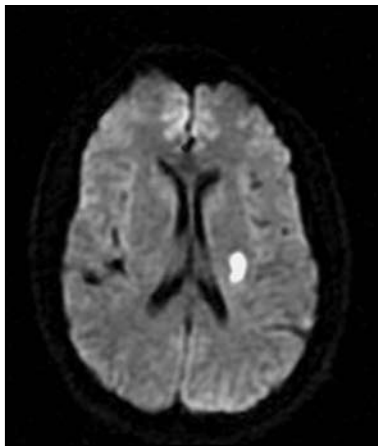
The DWI measures differences in the movement of tissue water molecules based on random Brownian motion of water molecules. The extent of water diffusion in tissue depends on the observation time as well as the presence or absence of barriers, such as cell membranes, organelles, or macromolecules. The apparent diffusion coefficient (ADC) represents the weighted average of intracellular and extracellular compartment diffusion coefficients, and is a measure of the relative freedom of water diffusion. Diffusion is slower in the intracellular space compared to the extracellular space, as the free movement of water is potentially obstructed by barriers at the molecular and cellular level. This may be represented by a diffusion weighted image, where areas of brain parenchyma with low ADC values due to restricted diffusion are rendered as areas of hyperintensity. This can also be represented on an ADC map, where the same area would be displayed as an area of decreased signal or hypointensity.^{1,18,26-28}

In ischemic stroke, one of the theories behind the restriction in water diffusion within areas of acute infarction is the shift of water from the extracellular compartment to the intracellular compartment, causing cytotoxic edema. Cytotoxic edema corresponds to high signal intensity on DWI due to restricted diffusion, while vasogenic edema causes low signal intensity on DWI due to increased diffusion. While there are cases of reversible diffusion abnormalities in the setting of hyperacute stroke, the area of increased signal on DWI in lesions of acute stroke is generally believed to represent the area of irreversible core of ischemic infarction. Clinical outcome in stroke has been correlated with the volume of the lesion within 48 hours in DWI.^{1,26-28}

Figure 5A. CT of a patient with acute right sided weakness, without definite acute abnormality.



Figure 5B. Diffusion weighted imaging obtained immediately following head CT in the same patient demonstrates well-delineated acute infarction involving the left corona radiata.



In animal experiments of DWI imaging of ischemic stroke, signal changes within brain parenchyma have been observed within two to three minutes.¹ While DWI generally reveals signal changes within 30 minutes in humans, case reports have revealed more rapid DWI identification of ischemic stroke, in as little as 11 minutes.^{1,29} The low diffusion signal on an ADC map and high signal intensity on DWI, resulting from ischemic stroke, lasts between 10 days and 2 weeks. In the chronic phase (>2 weeks), the ADC signal undergoes “pseudonormalization” and elevation due to encephalomalacia, with increased water diffusion and gliosis.^{1,25,30}

Imaging via DWI can help differentiate between acute and chronic stroke lesions as well. Both cytotoxic

edema secondary to acute infarction and gliosis secondary to chronic infarction have hyperintense signal characteristics on T2 weighted imaging. Although a lesion from a chronic infarction will have high signal on T2 weighted imaging, it will have an isointense signal to normal brain parenchyma on DWI, as opposed to a hyperintense signal on DWI in an acute infarction.^{1,25}

It is important that DWI imaging be correlated with T2 weighted images as well as the ADC map.³¹ Since most DWI imaging techniques have T2 weighting, the shine through effect may be observed. This effect causes lesions that have high signal intensity on T2 weighted imaging to be seen as areas of mild hyperintensity on DWI. In this instance, the ADC maps will correctly delineate between acute lesions, with lower signal intensity and chronic lesions, which will have higher signal intensity.¹

CT Angiography (CTA) and MR Angiography (MRA)

Both CTA and MRA provide noninvasive methods in the evaluation of cerebral vasculature in the setting of acute stroke.¹ The CTA and MRA can demonstrate the location of a lesion as well as provide further information as to the possible etiology of a thrombus or embolus, the site where thrombolysis may be targeted, as well as the patterns of collateral circulation to an area of affected parenchyma.²

There are three methods of MRA: time of flight (TOF), phase contrast (PC) and contrast enhanced angiography. The TOF technique is based on the flow related enhancement caused by protons which are not immediately exposed to a radio frequency pulse. This technique is sensitive to flow related enhancement which is predominant in slow or moderate flow. The PC technique tags moving spins in order to track positional change and create an angiographic image based on flow velocities. Contrast enhanced MRA involves the injection of paramagnetic contrast and the use of vascular enhancement to create a high resolution image of the intracranial vasculature.¹ Use of MRA has been demonstrated to identify proximal occlusions of large vessels, but it has not been as reliable in identifying occlusions in smaller, distal branches.²

The CTA involves the injection of iodinated contrast, followed by the acquisition of a 2-dimensional data set which is used to demonstrate the cerebral vasculature. The CTA is a rapid imaging modality, taking less than 30 seconds for the image to be acquired. However, the postprocessing of data acquired

by CTA involves significant time.¹ The CTA has been demonstrated to be effective in the evaluation of occlusions of large extracranial as well as intracranial vessels.²

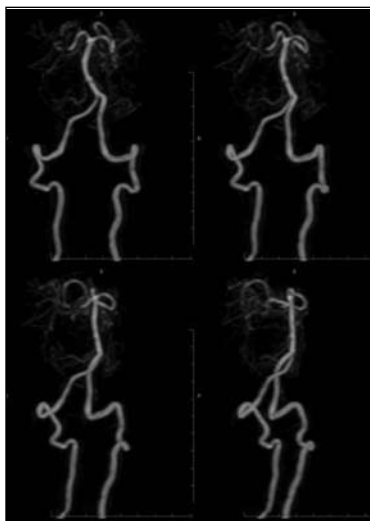
Figure 6A. Normal 3D time of flight brain MRA demonstrating major intracranial arteries in 3D, which can be rotated in space for detailed evaluation (Figure 6B).



Figure 6B.



Figure 6C. Post processed isolated images of vertebrobasilar arteries from a gadolinium bolus 3-D neck MRA.



Stroke Therapy and Implications on Imaging

While *in vitro* and *in vivo* experimental models have demonstrated several mechanisms of tissue damage in ischemic stroke which may be limited or delayed by neuroprotective medical treatment, none of these treatment approaches has been demonstrated to improve outcomes in multiple clinical trials. Therefore, current therapeutic interventions for acute stroke target rapid restoration of blood flow using intravenous or intra-arterial thrombolysis or mechanical thrombus extraction for preservation of brain parenchyma.^{7,32}

In 1995, The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group demonstrated that intravenous recombinant tissue plasminogen activator (rt-PA, alteplase), administered within three hours of a stroke, was associated with improved clinical outcome after three months when compared to placebo, although with increased risk of intracerebral hemorrhage. At 24 hours after the onset of stroke, there was no difference in neurologic improvement seen in patients treated with rt-PA and placebo. However, at three months follow-up, patients treated with rt-PA were found to have statistically significant clinical improvement (global odds ratio 1.7), and had an increased likelihood of having minimal to no disability of at least 30% compared to the placebo group. Intracerebral hemorrhage was observed in 0.6% of patients who were treated with placebo, while this complication occurred in 6.4% of patients who were administered rt-PA. After three months, mortality in the rt-PA treatment group was 17%, while in the placebo group, it was 21%. Based on the proven benefit of rt-PA in the NINDS trial, the Food and Drug Administration (FDA) approved the use of IV administration of recombinant tissue plasminogen activator for ischemic stroke in 1996.³³⁻³⁵

The Prolyse in Acute Cerebral Thromboembolism (PROACT) studies were randomized, controlled studies which evaluated the direct, trans-catheter intra-arterial administration of recombinant pro-urokinase (rpro-UK) into the body of a thrombus. In 1998, the PROACT I trial demonstrated that IA administration of rpro-UK (alteplase) aids in recanalization (57% of patients) of proximal MCA occlusion when administered within six hours of stroke onset, versus 14% of patients treated with placebo. Intracerebral hemorrhage was observed in 15% of patients treated with rpro-UK versus 7%, and was correlated with the concomitant dose of heparin.³⁶⁻³⁸

In 1999, the PROACT II trial demonstrated a 15% absolute and 58% relative increase in positive

outcomes in patients treated with IA rpro-UK. The PROACT II trial also demonstrated MCA revascularization in 66% of patients treated with IA rpro-UK, versus 18% of the control group. Intracerebral hemorrhage was observed in 10.9% of the treated group and in 3.1% of controls, although overall mortality was not significantly different between the two groups, with 25% and 27%, respectively.^{37,39}

The Interventional Management of Stroke (IMS) II Trial was a safety and feasibility study to obtain preliminary data for a randomized trial that compared the use of intravenous rt-PA with a combined intravenous and intra-arterial approach. The IMS II trial found that the mortality at three months was lower (16%) than patients treated with placebo (24%), as well as patients treated with rt-PA in the NINDS trial (21%). Intracerebral hemorrhage was observed in 9.9% of treated patients, which was not significantly different than patients treated with rt-PA in the NINDS trial. Additionally, patients who received treatment had better outcomes (global odds ratio ≥ 2.7) than placebo patients in the NINDS trial, as well as patients treated with rt-PA in the NINDS trial. The IMS II trial was followed with the currently ongoing IMS III trial, which aims to evaluate if a combined intravenous and intra-arterial rt-PA is superior to intravenous rt-PA in achieving the outcome of recanalization, if patients are treated within three hours of the onset of ischemic stroke.⁴⁰⁻⁴²

In 2005, the Mechanical Embolus Removal in Cerebral Ischemia (MERCİ) Trial revealed that an endovascular embolectomy device was able to restore blood flow in ischemic stroke within eight hours of the onset of symptoms. The MERCİ Trial demonstrated MCA revascularization in 45% of patients, when compared to the spontaneous recanalization rate observed in PROACT II. Procedural complications which caused clinically significant adverse effects were observed in 7% of patients, while fracture of the device, which occurred in 3% of treated patients, was correlated with the death of 2 patients (1.4%). Based on the results from the MERCİ Trial, the mechanical embolectomy device received FDA approval in 2004 in order to provide a therapeutic option for patients who do not meet the criteria for thrombolysis based on time frame or contraindications.^{43,44}

The development of thrombolytic therapy increases the necessity to reliably and rapidly identify stroke within the time limit in which the benefits of thrombolytic therapy have been demonstrated to outweigh its risks. Current imaging techniques should not only detect the presence of an acute infarction and possible

associated hemorrhage, but also ascertain the presence and measure the volume of ischemic penumbra, or area of ischemic but potentially salvageable tissue for appropriate selection of those patients who would benefit from such aggressive therapies without exposing patients to unreasonable risks. The development of MR diffusion and perfusion weighted imaging, as well as CT perfusion imaging, allows detection and identification of the extent of ischemic penumbra.

CT and MR Perfusion Weighted Imaging

The technique of perfusion weighted imaging (PWI) may be used in combination with diffusion weighted imaging to delineate the area of brain parenchyma affected by decreased blood flow, and to characterize the ischemic penumbra which therapy aims to preserve.

In ischemic stroke, the area of abnormal perfusion is thought to encompass the ischemic core, as well as the ischemic penumbra, which is at risk for death but which may be salvaged by reperfusion.¹ A CT and MR perfusion weighted imaging can characterize the change in blood perfusion to brain parenchyma according to several parameters. Relative cerebral blood volume (rCBV) is the volume of blood per unit of brain tissue, which is normally 4–5 mL/100 g. Mean transit time (MTT) is the difference in time between arterial inflow and venous outflow of blood, which has been measured to be between three to five seconds in cerebral cortical regions of normal subjects. Relative cerebral blood flow (rCBF) is calculated by the ratio of rCBV to MTT.^{1,18,26,45}

There are several techniques of MR perfusion imaging, including dynamic contrast-enhanced susceptibility-weighted perfusion imaging and arterial spin labeling techniques. The dynamic contrast-enhanced susceptibility technique tracks the passage of an injected bolus of an exogenous paramagnetic contrast agent (ie, gadolinium) through the brain as a series of T2 weighted images is acquired. The arterial spin labeling technique is an endogenous contrast technique which “tags” hydrogen-1 protons in water molecules within arterial blood to a slice, which can then be used to quantify blood flow using the perfusion parameters.^{1,46,47}

The most commonly used MR perfusion technique is the dynamic contrast-enhanced susceptibility technique. Information from this technique is used to generate a curve of signal intensity over time, which is converted to contrast concentration over time, and used to derive the perfusion parameters of rCBF, rCBV and MTT using a deconvolution technique.

This information is then used to generate perfusion maps of rCBV and MTT.^{1,45,47}

There are two methods of CT perfusion imaging; dynamic contrast-enhanced perfusion imaging and perfused blood volume mapping.⁴⁵ Dynamic contrast-enhanced perfusion CT uses the multicompartamental tracer kinetic model to track an injected bolus of iodinated contrast as it travels through the cerebral circulation.^{18,45} The injected bolus of contrast causes an increase in attenuation that is related to the amount of contrast in a ROI. This information is used to derive curves that represent attenuation over time for arterial and venous blood. The perfusion parameters can be subsequently derived from this information using deconvolution analysis. Information derived from dynamic contrast-enhanced perfusion imaging may also be used to generate color perfusion maps of rCBV, rCBF and MTT, in order to enable visual identification of areas of decreased perfusion.⁴⁵ In the past, the shortcoming of CT perfusion imaging was limited coverage of the brain, but with the latest software upgrades, the coverage area has increased to 8 cm, or sixteen 5 mm axial slices, which should cover most of the supratentorial brain.¹²

Images A-F of the insert nicely illustrate the application of advanced MR imaging techniques in the evaluation of acute stroke. These images depict an example of acute infarctions in a patient with underlying chronic microvascular ischemic disease. Diffusion weighted imaging clearly demonstrates new infarcts as areas of hyperintensity within a background of chronic white matter infarctions within cerebral hemispheres, primarily within the left cerebral hemisphere. Perfusion MRI demonstrates decreased relative cerebral blood flow and relative cerebral blood volume with increased mean transit time.

Conclusion

Computed Tomography and Magnetic Resonance Imaging have revolutionized the diagnosis and treatment of stroke in their ability to rapidly and accurately detect and localize the presence of an acute infarction. The development of diffusion-weighted imaging further shortened the time to diagnosis in acute ischemic stroke and increased the specificity of the diagnosis of a new stroke in the presence of old strokes.

The development of intravenous thrombolysis, intra-arterial thrombolysis and mechanical clot removal techniques has increased the range of therapeutic options for acute stroke patients. These techniques have been shown in multiple trials to improve the

outcome of the subgroup of acute stroke patients who meet appropriate treatment criteria. Advanced imaging techniques such as perfusion CT and MRI techniques hold promise in providing additional functional information about the physiologic state of an acute stroke patient in terms of cerebral blood flow, cerebral blood volume, and mean transit time. The use of these state-of-the-art imaging techniques can help correctly triage acute stroke patients to maximize the benefits of therapeutic interventions while minimizing the risks inherent to these interventions.

One of the most significant challenges in the therapy of acute stroke is in the timing of patient arrival to a treatment center. Studies have shown that approximately one fifth (22–27%) of patients arrive to an ED within the three hour time frame of stroke therapy, but only approximately 8% of ischemic stroke patients who arrive to an ED qualify for rtPA. There are many factors that contribute to the delay in arrival to an ED for acute care, including limited awareness of stroke signs and available treatment options by patients, as well as delays in emergent transport to a certified stroke center.^{48,49}

Today, rapid and accurate diagnosis and therapeutic intervention of acute stroke patients require an interdisciplinary and multidisciplinary approach in the setting of a comprehensive stroke program. In 2005, the American Stroke Association's Task Force on the Development of Stroke Systems emphasized the integration of multiple components in stroke prevention, treatment, and rehabilitation: primordial and primary prevention, community education, notification and response of emergency medical services, acute stroke treatment, including the hyperacute and emergency department phases, subacute stroke treatment and secondary prevention, rehabilitation, (and) continuous quality improvement (CQI) activities.⁵⁰

In 2005, the Brain Attack Coalition issued a recommendation statement on the establishment of acute stroke centers.⁵¹ This statement outlines the requirements for a comprehensive stroke center to be able to deliver specialized care for patients with cerebrovascular disease: (1) healthcare personnel with specific expertise in a number of disciplines, including neurosurgery and vascular neurology; (2) advanced neuroimaging capabilities such as MRI and various types of cerebral angiography; (3) surgical and endovascular techniques, including clipping and coiling of intracranial aneurysms, carotid endarterectomy, and intra-arterial thrombolytic therapy; and (4) other specific infrastructure and programmatic elements such as an intensive care unit and a stroke registry.

The statement concludes that a comprehensive stroke center which integrates these resources is likely to improve outcomes of patients who suffer from stroke and cerebrovascular disease.⁵¹

A comprehensive stroke center has several components that integrate these recommendations. First, it requires a widespread community-based educational program of the general population which aims to promote the reduction of risk factors for primary prevention of strokes as well as increase the early recognition of signs and symptoms of acute stroke. Second, it requires an organized EMS infrastructure that allows for a rapid transport of a patient to the stroke center. Finally, rapid clinical assessment and CT and MR imaging of the patient need to be performed to make the diagnosis of acute stroke and to assess location, size and perfusion state of brain parenchyma affected by stroke at the time of the patient's presentation. The combination of clinical and imaging information would be used to make appropriate treatment decisions which could include intravenous and/or intra-arterial thrombolysis or intra-arterial mechanical clot extraction.

Such a comprehensive approach to the prevention and acute management of ischemic stroke would require a significant investment in resources by institutions, as well as effective collaboration by physicians on an interdisciplinary stroke team in order to maximize the benefit and minimize the risk in the management of ischemic stroke patients. Ultimately, the establishment of comprehensive stroke centers should be justified by a population-based outcomes analysis that demonstrates the cost-effectiveness of such a program, based on an evaluation of resource utilization and final clinical outcomes in terms of the reduction in long-term morbidity and mortality in the acute stroke patient population.

Aleksandrs U. Kalnins is an MD/MBA student in the Medical Scholars Program at the University of Illinois at Urbana Champaign.

Dr. Thomas A. Kim is a neuroradiologist and head of the Division of Neuroradiology in the Department of Radiology at Carle Clinic Association.

References

1. Grossman RI, Yousem DM. *Neuroradiology: The Requisites*. Philadelphia, PA: Elsevier; 2003. p. 183-186.

2. Rowley HA. The four Ps of acute stroke imaging: parenchyma, pipes, perfusion, and penumbra. *AJNR Am J Neuroradiol*. 2001 Apr;22(4):599-601.

3. Smith WS, Johnston SC, Easton JD. Cerebrovascular diseases. In: Kaspar DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. *Harrison's principles of internal medicine*. 16th ed. New York: McGraw Hill; 2005. p. 2372-2393.

4. Messing RO. Nervous system disorders. In: McPhee SJ, Ganong WF, editors. *Pathophysiology of disease: an introduction to clinical medicine*. 5th ed. New York: McGraw Hill; 2006. p. 182.

5. Djang WT, Gray L, Drayer BP. Intracranial occlusive vascular disease. In: Taveras JM, Ferrucci JT, editors. *Radiology on CD-ROM: diagnosis, imaging, intervention*. Philadelphia (PA): Lippincott Williams & Wilkins; 2000.

6. van der Worp HB, van Gijn J. Clinical practice. acute ischemic stroke. *N Engl J Med*. 2007;357(6):572-579.

7. Lo EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. *Nat Rev Neurosci*. 2003;4(5):399-415.

8. Fishman RA. *Cerebrospinal fluid in diseases in the nervous system*. 2nd ed. Philadelphia (PA): W.B. Saunders; 1992.

9. Kim TA, Lindell PE, Prost RE. Magnetic resonance imaging of brain. In: Winn HR, editor. *Youman's neurological surgery*. Philadelphia (PA): Saunders; 2004. p. 463-466.

10. Castillo M, Scatliff JH, Kwock L, Green JJ, Suzuki K, Chancellor K, et al. Postmortem MR imaging of lobar cerebral infarction with pathologic and in vivo correlation. *Radiographics*. 1996;16(2):241-250.

11. Guyton AC, Hall JE. *Textbook of medical physiology*. 11th ed. Philadelphia (PA): Saunders; 2006. p. 761.

12. Muir KW, Buchan A, von Kummer R, Rother J, Baron JC. Imaging of acute stroke. *Lancet Neurol*. 2006;5(9):755-768.

13. Latchaw RE, Yonas H, Hunter GJ, Yuh WT, Ueda T, Sorensen AG, et al. Guidelines and recommendations for perfusion imaging in cerebral ischemia: A scientific statement for healthcare professionals by the writing group on perfusion imaging, from the Council on Cardiovascular Radiology of the American Heart Association. *Stroke* 2003;34(4):1084-1104.
14. Khurana VG, Benarroch EE, Katusic ZS, Meyer FB. Cerebral blood flow and metabolism. In: Winn HR, editor. *Youman's neurological surgery*. Philadelphia (PA): Saunders; 2004. p. 1468.
15. Moustafa RR, Baron JC. Clinical review: Imaging in ischaemic stroke - implications for acute management. *Crit Care* 2007;11(5):227.
16. Osborn AG. *Diagnostic neuroradiology*. St. Louis (MO): Mosby; 1994. p. 344-347.
17. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. *Alberta Stroke Programme Early CT Score*. *Lancet*. 2000;355(9216):1670-1674.
18. Choksi V, Quint DJ, Maly-Sundgren P, Hoeffner E. Imaging of acute stroke. *Appl Radiol* 2005;26(2):10-19.
19. O'Brien P, Sellar RJ, Wardlaw JM. Fogging on T2-weighted MR after acute ischaemic stroke: how often might this occur and what are the implications? *Neuroradiology* 2004;46(8):635-441.
20. Chalela JA, Kasner SE. The fogging effect. *Neurology*. 2000;55(2):315.
21. Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. *JAMA* 2004;292(15):1823-1830.
22. Essig M, von Kummer R, Egelhof T, Winter R, Sartor K. Vascular MR contrast enhancement in cerebrovascular disease. *AJNR Am J Neuroradiol* 1996;17(5):887-894.
23. Liebeskind DS. Collaterals in acute stroke: beyond the clot. *Neuroimaging Clin N Am* 2005;15(3):553-573, x.
24. Mathews VP, Rawley HA. "Comprehensive Imaging for Acute Stroke Imaging." Radiological Society of North America Scientific Assembly and Annual Meeting; 2007 November 30, 2007; McCormick Place, Chicago, IL.
25. Provenzale JM, Sorensen AG. Diffusion-weighted MR imaging in acute stroke: theoretic considerations and clinical applications. *AJR Am J Roentgenol*. 1999;173(6):1459-1467.
26. Schaefer PW, Ozsunar Y, He J, Hamberg LM, Hunter GJ, Sorensen AG, et al. Assessing tissue viability with MR diffusion and perfusion imaging. *AJNR Am J Neuroradiol* 2003 Mar;24(3):436-43.
27. Lansberg MG, Thijs VN, O'Brien MW, Ali JO, de Crespigny AJ, Tong DC, et al. Evolution of apparent diffusion coefficient, diffusion-weighted, and T2-weighted signal intensity of acute stroke. *AJNR Am J Neuroradiol*. 2001 Apr;22(4):637-44.
28. McGraw P, Mathews VP. Diffusion-weighted magnetic resonance imaging of cerebral ischemia. *Semin Cerebrovas Dis Stroke* 2001;1(4):326-330.
29. Hjort N, Christensen S, Solling C, Ashkanian M, Wu O, Rohl L, et al. Ischemic injury detected by diffusion imaging 11 minutes after stroke. *Ann Neurol* 2005;58(3):462-465.
30. Burdette JH, Ricci PE, Petitti N, Elster AD. Cerebral infarction: time course of signal intensity changes on diffusion-weighted MR images. *AJR Am J Roentgenol* 1998;171(3):791-795.
31. Baird AE, Warach S. Magnetic resonance imaging of acute stroke. *J Cereb Blood Flow Metab* 1998;18(6):583-609.
32. Green AR. Pharmacological approaches to acute ischaemic stroke: reperfusion certainly, neuroprotection possibly. *Br J Pharmacol* 2007;158:s325-338.
33. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995;333(24):1581-1587.

34. The Internet Stroke Center. Stroke Trials Directory: NINDS tPA. [cited January 12, 2008]; Available from: <http://www.strokecenter.org/trials/TrialDetail.aspx?tid=61>.
35. Adams HP, Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007;38(5):1655-1711.
36. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. *Prolyse in Acute Cerebral Thromboembolism*. *Stroke* 1998;29(1):4-11.
37. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Prolyse in Acute Cerebral Thromboembolism*. *JAMA* 1999;282(21):2003-2011.
38. The Internet Stroke Center. Stroke Trials Directory: PROACT I. [cited January 12, 2008]; Available from: <http://www.strokecenter.org/trials/TrialDetail.aspx?tid=28>.
39. The Internet Stroke Center. Stroke Trials Directory: PROACT II. [cited January 12, 2008]; Available from: <http://www.strokecenter.org/trials/TrialDetail.aspx?tid=46>.
40. IMS II Trial Investigators. The interventional management of stroke (IMS) II study. *Stroke* 2007;38(7):2127-2135.
41. The Internet Stroke Center. Stroke Trials Directory: IMS II. [cited January 12, 2008]; Available from: <http://www.strokecenter.org/trials/TrialDetail.aspx?tid=487>.
42. The Internet Stroke Center. Stroke Trials Directory: IMS III. [cited January 12, 2008]; Available from: <http://www.strokecenter.org/trials/TrialDetail.aspx?tid=747>.
43. Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke* 2005;36(7):1432-1438.
44. The Internet Stroke Center. Stroke Trials Directory: MERCI. [cited January 12, 2008]; Available from: <http://www.strokecenter.org/trials/TrialDetail.aspx?tid=619>.
45. Srinivasan A, Goyal M, Al Azri F, Lum C. State-of-the-art imaging of acute stroke. *Radiographics* 2006;26 Suppl 1:S75-S95.
46. Ibaraki M, Ito H, Shimosegawa E, Toyoshima H, Ishigame K, Takahashi K, et al. Cerebral vascular mean transit time in healthy humans: a comparative study with PET and dynamic susceptibility contrast-enhanced MRI. *J Cereb Blood Flow Metab* 2007;27(2):404-413.
47. Yamada K, Wu O, Gonzalez RG, Bakker D, Ostergaard L, Copen WA, et al. Magnetic resonance perfusion-weighted imaging of acute cerebral infarction: effect of the calculation methods and underlying vasculopathy. *Stroke* 2002;33(1):87-94.
48. Rowley HA. Extending the time window for thrombolysis: evidence from acute stroke trials. *Neuroimaging Clin N Am* 2005;15(3):575-87, x.
49. Kleindorfer D, Kissela B, Schneider A, Woo D, Houry J, Miller R, et al. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. *Stroke* 2004;35(2):e27-e29.
50. Schwamm LH, Pancioli A, Acker JE, 3rd, Goldstein LB, Zorowitz RD, Shephard TJ, et al. Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems. *Stroke* 2005;36(3):690-703.
51. Alberts MJ, Latchaw RE, Selman WR, Shephard T, Hadley MN, Brass LM, et al. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. *Stroke* 2005;36(7):1597-1616.

CME Questions 2a-d

Please select the best answer for the following:

- 2a. The main goal of imaging in ischemic stroke is to:
 - a. Diagnose ischemic stroke
 - b. Exclude non-ischemic stroke
 - c. Rule out brain tumor
 - d. All of the above

- 2b. Ischemic injury of brain parenchyma is a result of energy depletion.
 - a. True
 - b. False

- 2c. Within 24 hours of an ischemic event an indistinct area of low density develops in the distribution of occluded vessel.
 - a. True
 - b. False

- 2d. Diffusion weighted imaging cannot differentiate between acute and chronic stroke lesions.
 - a. True
 - b. False