Stroke is one of the most common neurological disorders in clinical practice. An estimated 5.7 million patients died from stroke in 2005, with 87% of these deaths occurring in low- and middle-income countries. Globally, stroke is the third leading cause of death and a major cause of adult disability. It poses serious medical, socioeconomic, and rehabilitation problems. With the prevalence of disability resulting from stroke expected to rise as populations increase and now survive through their peak years, this burden will increase greatly over the next 20 years, particularly in developing countries. Stroke physicians are faced with the challenge of providing effective stroke care and reducing the mortality, disability, and dependency of stroke survivors. In the last 15 years, significant advances have been made in the treatment of acute stroke. Four specific strategies have emerged that have proven ability to improve outcomes: the administration of tissue plasminogen activator (tPA), aspirin, stroke care units (SCU), and decompressive surgery for supratentorial malignant hemispheric cerebral infarction.

A reanalysis of the first major study of tPA in acute ischemic stroke, the NINDS trial, has confirmed the effectiveness of intravenous thrombolysis if administered within 3 h of stroke onset. Later studies showed that intravenous tPA can possibly be safely given beyond 3 h in patients with a penumbra, and hence the importance of delineating ischemic penumbral tissue using quick and effective imaging techniques.

The use of brain imaging helps clinicians to make early management decisions with regard to aspirin or thrombolysis in acute stroke, antiplatelet agents, statins, blood pressure lowering with ACE inhibitors, anticoagulants, statins and carotid endarterectomy or...
stenting for secondary prevention.\(^{11-12}\) In addition to its use in the early diagnosis of stroke and in the exclusion of intracerebral hemorrhage (ICH), an emerging potential application of neuroimaging in stroke is in the selection of patients for reperfusion therapies. This is done by identifying patients with salvageable cerebral tissue, a low risk of hemorrhagic transformation, or occlusion of large arteries that might or might not be amenable to therapy.

This has been largely possible due to the introduction of CT, CTP, CTA, and MRI with DWI sequences, gradient echo, and MR angiography (MRA). While CT has been the workhorse of stroke diagnosis over the last 20 years, it is now apparent that MRI is as useful, if not more so.\(^ {13,14}\)

**Imaging brain parenchyma**

**Noncontrast CT (NCCT)**

Ischemic strokes constitute 80% of all strokes, 15% are hemorrhagic strokes, and almost 5% are due to subarachnoid hemorrhage (SAH).\(^ {15-17}\) It is not always possible to differentiate ischemic strokes from hemorrhagic strokes on clinical grounds. NCCT is still the mostly commonly used initial imaging modality in hyperacute stroke.\(^ {18}\) NCCT is widely available, besides being quick and easy to perform in most stroke patients. It accurately identifies ICH as well as SAH as soon as it has occurred. It also depicts the topography of hemorrhages and any mass effect, hydrocephalus, and intraventricular extension. However, the hemorrhages which are initially hyperdense become indistinguishable from cerebral infarction within 10-14 days in up to three-quarters of the cases. This can be misleading, and after 2 weeks CT is not a useful technique to distinguish between old infarction and hemorrhage.\(^ {19}\) Another disadvantage is that it cannot detect petechial hemorrhages in patients with very low hemoglobin levels. However, NCCT helps in differentiating ischemic stroke from stroke mimics, which can be present in about 4% of stroke patients.\(^ {20}\)

The early signs of cerebral ischemia on CT scan have been well described in middle cerebral artery (MCA) strokes; they include [Table 1]:

- Hyperdense MCA artery sign and the MCA ‘dot’ sign\(^ {21-23}\)

**Table 1: Early computerized tomography changes in noncontrast computed tomography.**

| Hyperdense artery sign | Hyperdense dot sign | Hypodensity of insular ribbon | Hypodensity of basal ganglia | Loss of grey-white matter differentiation in cortical ribbon | Sulcus effacement |
|-----------------------|---------------------|-------------------------------|-------------------------------|-------------------------------------------------|------------------|

The early signs of cerebral ischemia on CT scan have been well described in middle cerebral artery (MCA) strokes; they include [Table 1]:

- Hyperdense MCA artery sign and the MCA ‘dot’ sign\(^ {21-23}\)

- Hypodensity of insular ribbon outline and basal ganglia\(^ {24,25}\)

- Loss of grey-white matter distinction in the cortical ribbon and lentiform nucleus and effacement of the sulcus\(^ {26}\)

The hyperdense artery sign indicates thrombus or embolus in the M1 part of the MCA, while the MCA dot sign is indicative of thrombosis of the M2 or M3 branches of MCA. The other subtle early CT signs are due to parenchymal hypodensity or focal swelling, which reflects cytotoxic edema and manifests in the form of reduced visibility of sulci and ventricles.\(^ {127}\) The presence of early CT changes has been found to be associated with a poor prognosis. A very large parenchymal hypodensity involving more than one-third of the MCA territory and with early CT changes has been considered a relative contraindication for thrombolysis. This was largely based on the ECASS I study, which revealed increased risk of hemorrhagic transformation with thrombolytic therapy in patients having signs of early infarction in more than one-third of the MCA territory.\(^ {28}\) However, in NINDS trial and in the Australian Streptokinase Trial (ASK), there was no relationship between early CT changes and increased intracerebral hemorrhages in patients treated with thrombolytic agents.\(^ {29,30}\) Similarly, a hyperdense MCA artery has been found to be associated with a poor outcome and an increased risk of hemorrhage following thrombolysis in a general stroke population.\(^ {31,32}\) It has been argued that the poor prognosis in these patients might well have been due to delay in starting treatment rather than the early CT changes.\(^ {33}\)

The early CT signs are often difficult to identify in the first few hours after stroke onset. There is also considerable interobserver variability.\(^ {34}\) This has partly been overcome by the development of the Alberta Stroke
Programme Early CT Score (ASPECTS) which was proposed in 2001.\textsuperscript{35} Quantitative assessment of acute ischemia in the MCA territory on CT can be made on a 10-point topographic scoring system. A normal MCA territory is given a score of 10, and diffuse ischemia in most of the MCA region a score of 0. Logically, the baseline ASPECTS has been found to correlate inversely with baseline NIHSS. Further, ASPECTS, along with some clinical information, has also been found to be predictive of response to thrombolysis.\textsuperscript{36-37} Very low ASPECTS scores have been shown to be associated with an increased risk of ICH in the ECASS II cohort and with a poor outcome in the NINDS cohort.\textsuperscript{38}\n\nNCCT is relatively insensitive for the detection of acute small cortical or subcortical infarctions, especially in the posterior fossa.\textsuperscript{39,40} A follow-up NCCT is usually not required in stroke imaging unless the patient worsens neurologically, but it is required in patients treated with tPA to identify hemorrhagic transformation of cerebral infarction. Contrast-enhanced CT scan is not particularly useful for the diagnosis of acute stroke as it does not provide any additional information and may not detect infarction in the first few days due to a fogging effect.\textsuperscript{41}\n\nCT is the imaging modality of choice in SAH, being capable of detecting 98-100\% of cases within 12 h of symptom onset, particularly with thin sections.\textsuperscript{42} As with cerebral hemorrhage, CT cannot detect SAH precisely in patients with low levels of hemoglobin or after 2-3 weeks of onset of SAH. Cerebral venous sinus thrombosis (CVT) is commonly seen in young adults in developing countries. CT can show cord signs due to thrombosed cortical veins.\textsuperscript{43} The other CT features diagnostic of venous sinus thrombosis are the empty delta sign and the dense triangle sign corresponding to thrombosis in superior sagittal sinus.\textsuperscript{44} CT venography is increasingly used these days to diagnose CVT reliably and quickly.\textsuperscript{45}\n\n**Stroke MRI**\n\nSince its first use in clinical practice in 1984, MRI has created a significant shift in the management of neurological disorders. It is not only a diagnostic tool but also a surrogate end point for development of new therapies. MRI is very helpful for acute ischemic stroke in the clinical setting and for therapeutic decision making with regard to the use of thrombolysis. A comprehensive evaluation of stroke can be done by stroke MRI, which includes conventional MRI, MRA, and DWI.\n\nMR sequences used for acute stroke include T1-weighted spin-echo, T2-weighted spin-echo, fluid-attenuated inversion recovery (FLAIR), and T2-weighted gradient-echo. The T2-weighted spin-echo and FLAIR sequences show hyperacute ischemic tissue as hyperintense signals with loss of grey-white matter differentiation and sulcal effacement, similar to that seen with CT. Hyperintense arteries can also be seen on the FLAIR sequence as a high signal and as a low signal on T2-weighted gradient-echo. These changes, which are representative of direct thrombus visualization, are not only of diagnostic importance but also of prognostic significance. For example, it has been shown that the hyperintense artery sign is suggestive of fibrin-rich emboli and is independently predictive of recanalization.\textsuperscript{46} MRI has been shown to have diagnostic superiority over CT with comparable specificity (98\% CT vs 97\% MRI) for acute ischemic stroke, but MRI has much higher sensitivity (26\% CT vs 83\% MRI).\textsuperscript{47} There is also lower inter-rater variability with MRI in the diagnosis of acute stroke in first few hours as compared to conventional CT.\textsuperscript{43,47,48} However conventional MRI is less sensitive than DWI imaging in hyperacute stroke, the latter being an essential part of MR stroke imaging protocols.\textsuperscript{49} MRI is particularly useful for ischemic lesions, vessel occlusions, and pathology in the posterior circulation.\n\nMRI has been compared to CT in the detection of ICH, and has been shown to be as effective as CT in detecting ICH in the acute setting.\textsuperscript{43,51} T2-weighted gradient-echo can also detect microbleeds, which remain visible for longer periods. These clinically silent microbleeds are known to pose a 3\% risk of intracranial hemorrhage and may be associated with an increased risk of hemorrhage after thrombolysis, although this latter relationship needs substantiation in studies with large numbers of patients.\textsuperscript{52,53} Most often these microbleeds are chronic and are not visible on CT.\n\nMRI along with MRV is the imaging modality of choice in patients with suspected cerebral venous thrombosis (CVT). MR can differentiate between venous and arterial infarcts by detecting the presence of vasogenic edema or hemorrhage, which is commonly seen in the early stages of venous infarcts. Similarly, MRI along with MRA is the investigation of choice in patients with arterial dissection.\textsuperscript{54} However, its use is limited by time constraints; complaints of claustrophobia; and the presence of clipped or coiled aneurysms, ferromagnetic elements, pace makers, cochlear implants, and prosthetic valves in some cases.\n\nThe optimal MRI stroke protocol includes DWI, which shows acute lesions within minutes of onset of ischemia. DWI is unique in its ability to probe tissue microarchitecture at a cellular level due to its sensitivity to the motion of water molecules on the scale of a few microns.\textsuperscript{55} The mean diffusivity is of particular interest in the imaging of acute stroke, as changes can be observed minutes after onset of ischemia, and hours
before any changes can be observed using conventional imaging techniques.

Diffusion imaging assesses the relative mobility of water molecules. In acute ischemic stroke, water is redistributed from the extracellular to the intracellular space, thereby restricting water diffusion. The signal detected is high (bright) because water molecules cannot diffuse very far; while in normal healthy parenchyma, water diffuses more readily and the signal returned is lower (grey or black). However, sometimes, bright regions of T2-weighted images which are not diffusion-restricted signals persist in DW images, a phenomenon known as ‘T2 shine-through.’ Apparent diffusion coefficient (ADC) maps can be constructed to display actual diffusion coefficients (diffusion-restricted water). ADC maps show diffusion-restricted areas as dark, while regions of T2 shine-through on DWI imaging remain bright even on ADC maps. Thus, acute ischemic lesions are characterized by high-density bright lesions on DWI and low-intensity dark lesions on ADC maps [Figure 2]. Lesion size on DWI is a good predictor of final infarct volume.[57] DWI is also sensitive in detecting infarcts caused by microemboli during carotid endarterectomy or carotid stenting.[38,59] DWI can also depict various anterior circulation infarcts immediately after stroke onset, which may assist management of cases by enabling recognition of set patterns associated with specific stroke mechanisms. These include cortical, subcortical, territorial, watershed (or border zone), or even shower patterns of infarcts.[60] Additional information about the mechanism of stroke may be derived from DWI and other MR sequences (eg, multiple vascular territories suggest cardiac source of embolism); some information about location of stroke is also available (eg, posterior vs anterior circulation). This immediate and comprehensive information can then guide clinicians in early investigation and management, including thrombolysis.[61]

**Imaging cerebral vasculature**

**CT angiography (CTA)**

CTA provides valuable information on cerebral and extracranial vasculature; it is useful for the detection of thrombus in intracranial vessels, for the evaluation of carotid and vertebral arteries in the neck, and for guiding appropriate therapy. CTA involves scanning the vasculature from the aortic arch to the circle of Willis following a single intravenous bolus of nonionic contrast, generating three-dimensional, multiplanar, reformatted, angiographic images with excellent spatial resolution. CTA is particularly useful in guiding intra-arterial thrombolysis and mechanical thrombolysis. Parsons and his colleagues have shown that CTA source image ASPECTS more closely predicts the final infarct volume than NCCT ASPECTS.[62] CTA is usually combined with NCCT and CT perfusion, which collectively form multimodal stroke imaging (vide infra). The safety and feasibility of CTP and CTA following NCCT has been studied and do not show any significant adverse outcomes.[63] However, these procedures should be done with caution in patients who have diabetes, renal impairment, hypersensitivity to contrast agent, and cardiac decompensation. In hyperacute stroke, CTA provides important diagnostic information regarding the cerebral vasculature [Figure 3].

**MRA**

MRI is a useful noninvasive technique to evaluate extracranial as well as intracranial vessels to determine the site of occlusion or dissection. It has 90% sensitivity and specificity for extracranial carotid disease.[64] It is particularly useful in providing information regarding the mechanism of the stroke. MRA is rapid; does not require use of contrast, as in time-of-flight (TOF) MRA; and can image arteries as well as veins. In addition to TOF, MRA can also be obtained by injecting contrast (contrast MRA; which is very similar to CTA), and also by the phase-contrast (subtraction) method. The latter method of MRA is time consuming and not commonly employed in routine clinical practice.

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**Figure 2:** Hyper intense DWI lesion in left middle cerebral artery territory at three hours of stroke onset in a 34 year old patient (left panel) and quantifiable Apparent Diffusion Coefficient (ADC) map of same patient (right panel)

**Figure 3:** CT angiogram (CTA) of 83 an year old man showing right internal carotid artery occlusion just distal to the bifurcation
TOF MRA is noninvasive and is performed without contrast injection. Hence, this is the preferred method for use in combination with DW1-PW1 in acute stroke evaluation. Time of Flight Magnetic Resonance Angiography (TOF MRA) uses very rapid radio frequency pulses and signal detection. Signals from tissues that are not blood related are suppressed by saturation techniques. Hence, fresh blood flowing through saturated tissue appears bright against the very small signal from saturated tissues.\textsuperscript{[65]} It reliably detects internal carotid occlusion and anterior as well as basilar artery occlusion [Figures 4 and 5].

Contrast-enhanced MRA (CEMRA) is commonly used for visualizing vessel lumen. It is again a dynamic technique using timed bolus and bolus tracking method. Contrast Enhanced MRA (CEMRA) has been reported to be equivalent to DSA in assessing carotid artery stenosis before carotid surgery.\textsuperscript{[66]} It is more accurate than TOF MRA and provides higher-quality images.

Figure 4: Time of flight MRA of 83 year old man showing right internal carotid artery occlusion

Figure 5: Time of flight MRA of a 67 year old woman showing top of basilar arterial occlusion

However, the main limiting factor for its use is the need for administration of intravenous contrast.

The usefulness of MRA in imaging vessel occlusion and stenosis has been compared with that of Doppler ultrasonography and CTA. MRA and Doppler ultrasound (US) have been shown to have similar diagnostic performance in detecting carotid artery occlusion and > 70% stenosis.\textsuperscript{[67]} It has a pooled sensitivity of 95% and specificity of 90% for the diagnosis of > 70% stenosis as compared to Doppler US with a sensitivity of 86% and a specificity of 87%.\textsuperscript{[68]} MRA has been found to have 98% sensitivity and 100% specificity for detecting occlusion as compared to the 96% sensitivity and 100% specificity seen with Doppler US. The latter, however, is highly operator dependent. A combination of MRA (both TOF and CEMRA) and Doppler US has been reported to have a diagnostic accuracy equivalent to that of DSA.\textsuperscript{[69,70]} CTA is also an alternative technique to validate Doppler US and has also been compared with DSA in carotid artery disease. CTA has sensitivity and specificity of 97% for detecting occlusion and 85% sensitivity and 93% specificity for detecting stenosis of 70-99%.\textsuperscript{[71]} It has been shown that all three (CTA, MRA, and Doppler US) are equally suitable for evaluation of carotid stenosis with an overall sensitivity and specificity of about 80 to 90%, respectively, thus obviating the need for preoperative DSA. However DSA is required if there is any discrepancy in the findings or if the results of CTA, MRA or Doppler US are inconclusive.\textsuperscript{[60]}

**Ischemic penumbral imaging**

Imaging of the ischaemic penumbra has added a new dimension to the assessment of patients in the acute phases of stroke, but has not yet reached the stage of being used in routine clinical practice. The ischemic penumbra, as originally defined by Astrup, is a region of hypoperfused, electrically silent, and functionally impaired, but viable tissue.\textsuperscript{[72,73]} It is a concept based on animal experiments, in which lowered perfusion beyond a certain critical threshold leads to functional disturbances that are potentially reversible. It is a dynamic process of impaired perfusion and metabolism that extends from the ischemic core to the surrounding tissue. The penumbra corresponds to ischemic brain tissue, with diminished cerebral blood flow that has not yet led to complete infarction, and is potentially salvageable. Physiologically, reduction of mean cerebral blood flow of 50 ml/100 g/min to less than 20 ml/100 g/min, results in impaired neural function but preserved tissue integrity. The penumbra has an uncertain fate, its return to normalcy depending on reperfusion-achieved either spontaneously or therapeutically.\textsuperscript{[74]}

The ischemic penumbra has been the subject of intense
Core, penumbra and benign oligemia

Figure 6: The absolute cerebral blood flow in the treatment of acute ischemic stroke. Potential and is one of the key targets for intervention by DWI. It may be theoretically possible to extend the time window beyond 12 h based on the observation that spontaneous salvage of penumbra within the 12-48 h time interval is associated with improved clinical outcomes. [76] There are ongoing studies, in which investigators are testing the general hypothesis that patients selected with significant proportions of penumbra (based on imaging with MR or CT) and given thrombolytic therapy after the 3-h time window will respond favorably. [77,78] This emphasizes that the ischemic penumbra has recovery potential and is one of the key targets for intervention in the treatment of acute ischemic stroke.

CT perfusion (CTP)
The advent of the multidetector scanner has made it possible to rapidly scan with perfusion sequence, providing additional information on the penumbra and infarct core size. CTP is a functional brain imaging modality to characterize cerebral perfusion status by means of a set of parameter maps derived from dynamic contrast bolus study. The x-ray density of the brain temporarily increases following the administration of intravenous contrast. Information on cerebral blood flow (CBF) can be inferred from the extent and course over time of this increase in density. Parameters denoting cerebral perfusion can be calculated using various mathematical algorithms and can be represented in the form of color-coded parameter images. The central volume principle of cerebral hemodynamics is the basis for evaluation of brain perfusion. It is defined as the CBF being simply related to cerebral blood volume (CBV) and mean transit time (MTT) of the contrast bolus through the cerebral capillary network [Table 2]. The mathematical algorithms are based on gamma variate fit, which simply means first-pass bolus evaluation, with each voxel being a compartment with single input function and single output.

CTP scans can be done immediately following NCCT and take only a few minutes. This involves an intravenous bolus injection of about 50 ml of nonionic contrast at the rate of 5 ml/s using a power injector. Four sections of 8-12 mm are taken at the basal ganglia level, giving a spatial coverage of 32-48 mm in the supratentorial region. However, with the current scanners it is possible to cover a larger area of brain. Perfusion imaging data is obtained by the generation of arterial and venous time-attenuation curves. Determination of the arterial input function (AIF) enables investigators to isolate the true tissue response from the measured parenchymal density. Deconvolution analysis of these curves gives the MTT, CBV, and CBF. [79] Based on the basic deconvolution principal from the automatically generated source image (PCT SI), parametric maps of CBF, CBV, and MTT can be obtained [Figure 7].

The perfusion maps can then be assessed with a quick analysis for color changes that indicate a perfusion deficit. CBF reduction to 66%, CBV to less than 2.4 ml, and increase of MTT to 145% denotes the infarct core and CBV-CBF mismatch along with prolonged MTT denotes the penumbra. [80] It has also been shown that CBF and CBV obtained from CTP are sensitive and specific for infarction and useful for differentiating between penumbra and infarct [81] [Table 2]. However, detailed quantitative assessment of perfusion thresholds are still evolving. CTP source image improves identification of early ischemic changes in acute stroke. [82] There is also evidence that ASPECTS on CTP provides an accurate prediction of clinical outcome, as well as a rapid, reproducible assessment of the extent of both irreversibly ischemic and at-risk, but potentially salvageable, tissue in thrombolysis-eligible patients. [83] CTP imaging has been

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**Figure 6: A schematic representation of the Ischaemic Penumbra and the absolute cerebral blood flow values associated with the infarct core, penumbra and benign oligemia**
found to be more accurate than NCCT for detection of hemispherical strokes and is highly reliable for assessing the extent of stroke damage. CTP may become particularly useful in decision making when the time of onset is unknown, as in those awakening with stroke. Multimodal CT stroke imaging is easy to perform, widely available, quick, safe, and feasible in most hospitals. However, CTP is still a part of research protocols in many hospitals and yet to be used routinely in clinical practice. There is also a considerable interobserver variability as it is operator dependent, particularly with regard to the postprocessing of CTP data. Nonetheless, it is a promising technique and of great importance in developing countries.

**Perfusion MRI**

DWI can help identify infarct location within minutes, and to do so most accurately. However, it is questionable whether it alone can differentiate reversible from irreversible ischemic injury. This can be largely overcome by combining DWI with perfusion MRI. PWI is most useful for identifying reversible ischemic cerebral tissue. PWI can either be performed by administration of a MR contrast agent or by labeling of hydrogen-1 proton in water, which is known as arterial spin labeling. The MR contrast perfusion study involves tracking tissue signal changes following contrast bolus injection and plotting the time-signal intensity curve. The perfusion maps can then be calculated from this curve by using a deconvolution technique similar to that in CTP. By using PWI, disturbances of CBF as well as of CBV can be identified in the cerebral vasculature.

PWI is currently performed at selected centers with bolus contrast technique and provides qualitative measurements of CBF. The perfusion maps can be developed based on MTT or time-to-peak delays as compared to the normal hemisphere. A PWI-DWI mismatch, which indicates tissue with decreased perfusion, extending beyond that of diffusion abnormality is thought to represent tissue at risk of infarction but potentially salvageable. Currently, this is the most accepted method for identifying ischemic penumbra. DWI-PWI abnormality within the region of PWI abnormality, and without a DWI abnormality, is assumed to represent the penumbral region. This approach for identifying salvageable cerebral tissue in acute ischemic stroke is widely used in centers that perform acute stroke MRI. It has also been shown that abnormal PWI volumes have higher correlation with stroke severity as evaluated by NIHSS.

In most large-vessel strokes with an ischemic penumbra, the DWI lesion is smaller than the PWI regions (DWI-PWI mismatch). The lesions with both diffusion as well as perfusion abnormalities represent irreversible infarcted cerebral tissue, while regions with only perfusion abnormalities most likely represent the viable ischemic cerebral tissue-the penumbra. A large DWI lesion with proximal MCA occlusion is predictive of the development of the malignant MCA syndrome. This usually is the case in acute or subacute strokes with complete infarction and no penumbra. Another scenario of DWI-PWI imaging is the presence of only diffusion abnormalities (with normal perfusion) or the diffusion abnormality being larger than the perfusion abnormality. Both of these situations represent early spontaneous reperfusion of ischemic cerebral tissue and hence may be inappropriate for thrombolysis.

Table 2: Perfusion parameters on CT perfusion

| Parameter | Infarct Core | Penumbra |
|-----------|--------------|----------|
| CBV       | Less than 2.5 ml/100 gm | More than 2.5 ml/100 gm |
| CBF       | -            | Less than 66% of contra lateral side |
| MTT       | -            | More than 145% of contra lateral side |

CBF: Cerebral blood flow, CBV: cerebral blood volume, MTT: mean transient time.
selection of patients for thrombolytic therapy based on the presence or absence of tissue at risk. This approach has been explored in the recently published DEFUSE study in which MR mismatch was assessed in patients receiving tPA therapy. The investigators showed that for stroke patients treated 3-6 h after onset, baseline MRI findings can identify subgroups that are likely to benefit from reperfusion therapies and can potentially identify subgroups that are unlikely to benefit or may be harmed.[93] In centers where the time window for thrombolysis has been extended using MR mismatch techniques, the proportion of all stroke patients treated ranges from 10-25%.[94]

CTP has been shown to be comparable to DWI-PWI MRI for evaluation of the ischemic penumbra.[95] In hyperacute stroke, the combination of CTP and CTA renders important diagnostic information regarding infarct extent, perfusion deficit, and cerebral vasculature. It has been shown that the combination of NCCT, CTP, and CTA can provide additional information within 15 min and may be as helpful as MR for therapeutic decision making. Thus, the most accurate assessment of the site of occlusion, infarct core, salvageable brain tissue, and collateral circulation in patients suspected of acute stroke is afforded by combination of CTP and CTA.

However, MR perfusion has several advantages when compared to CTP. First, it covers the whole brain rather than only the 2-4 cm that is possible with CTP. Second, since it is invariably performed with DWI, the penumbral region with a mismatch is more readily visualized. Third, it identifies tissue at risk with more volumetric precision, thus enabling an accurate prediction of the final infarct volume and clinical outcome.[96-98] It is particularly helpful in stroke patients in whom CTP is not feasible, such as patients with diabetes mellitus or those with renal failure. However, it is more time consuming, which is often a critical issue in acute stroke management. One important requirement for the efficient integration of these techniques into clinical practice is the availability of trained staff around the clock.

An imaging-based pathophysiological diagnosis is increasingly being incorporated in the management of acute stroke patients in many centers in clinical trials involving thrombolysis; however, its true impact will not be appreciated until the results of trials of thrombolysis beyond the 3-h time window become available. Similarly, advanced MRI techniques like MR spectroscopy and diffusion tensor imaging are promising modalities to further delineate early ischemia, penumbra, and secondary Wallerian degeneration, but a discussion of these modalities is beyond the scope of this article.[99,100]

**Positron emission tomography (PET)**

PET usually involves the administration of a radioactive tracer (usually by intravenous injection) to quantify CBF, CBV, cerebral glucose metabolism, and neuroreceptor and neurotransmitter binding. A tracer is usually a biological compound of interest labeled with a positron emission isotope, such as C11, F18, or O15.[101] When quantitative data is required to generate images of CBF, oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen consumption (CMRO2), intra-arterial blood sampling is required. This PET technique has been considered as the gold standard for identification of infarct core and penumbra and has contributed significantly to the approach to reperfusion therapy in acute ischemic stroke. It has been shown by PET studies that substantial cortical penumbra can be detected in one-third of patients at 5-18 h, or even up to 48 h, using classical triple-tracer, hypoxic markers such as FMISO or neuronal markers such as flumazenil.[77,102-105] This was one of the first drivers for the view that the therapeutic time window for thrombolytic strategies could be different in certain stroke patients, with a possible extension of the time window.[106] PET is also being evaluated for its role in cerebral hemorrhage, particularly in cerebral amyloid angiopathy hemorrhage (CAAH), using 11C PIB PET. It has been shown that 11C PIB uptake is higher in patients with CAAH when compared to normal age-matched controls. 11C PET may be useful in in vivo diagnosis of CAAH and has the potential to serve as a surrogate marker for future therapeutic studies.[107]

Although PET is the gold standard for the detection of the ischemic penumbra and infarct core, it cannot be used for evaluation of cerebral vasculature, e.g., for studying intracranial or extracranial vessel occlusion or stenosis. Its use is also limited in the clinical setting in detecting nonvessel lesions causing stroke. In addition, it is costly, not available at all times, and is impractical for use in the evaluation of acute stroke in most centers specializing in acute stroke management.

**Single photon emission computed tomography (SPECT)**

SPECT has been used for the evaluation of cerebral perfusion in acute stroke for the last 2 decades. However, its use in refining patients for thrombolysis is somewhat unidimensional since it can only generate images of cerebral perfusion and these are only semiquantitative. However, valuable contributions to our understanding of the ischemic process have been made. The first clear demonstration that reperfusion was associated with better clinical outcomes was made using Tc-99m HMPAO SPECT.[108] Data was produced to show that ethyl cysteinate dimer (ECD) SPECT could be used within 6 h of stroke onset to identify patients likely to develop malignant MCA infarctions. These patients were
likely to worsen after thrombolysis and have a poor outcome and may be candidates for decompressive craniectomy. Similarly, normal SPECT in the first 3 h was an indication of likely spontaneous recovery without thrombolysis. However, its routine use in clinical practice is limited by the time constraints of acute stroke management and the introduction of more practical imaging tools such as CTP and MR DWI/PWI.

Conclusions

Stroke imaging has undergone significant advances over the last decade. It remains crucial for management of hyperacute stroke in first few hours, where the aim is to identify patients eligible for thrombolytic therapy and expected to have a good outcome. NCCT remains the first choice for ruling out cerebral hemorrhage and stroke mimics and for guiding thrombolysis in developing countries. Stroke MRI, particularly DWI/PWI, is the imaging technique of choice for the identification of infarct core and ischemic penumbra. This approach has the potential to assist in therapeutic decision making, particularly in the 3-6 h time window, but it has yet to find a place in routine clinical practice. MRA and CTA are important noninvasive imaging modalities for evaluation of the carotid and cerebral vasculature, along with Doppler US. Multimodal CT stroke imaging, which includes NCCT, CTP, and CTA, is frequently being used to enhance acute stroke diagnosis in many centers. This holds promise for countries like India where it is widely available, easy to use, and may help refine the decision for intervention even when the time of stroke onset is uncertain.

References

1. McMahon S. The global burden of stroke. In: Chalmers J, editor. Clinician’s manual on blood pressure and stroke prevention. London: Science Press; 2002. p. 1-6.
2. Strong K, Mathers C, Bonita R. Preventing stroke: Saving lives around the world. Lancet Neurol 2007;6:182-7.
3. Murray CJ, Lopez AD. Global mortality, disability and distribution of risk factors: Global burden of disease study. Lancet 1997;349:1436-42.
4. Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolytic therapy versus control in acute ischemic stroke. Cochrane Database Syst Rev 2003;3:CD000213.
5. CAST (Chinese Acute Stroke Trial) Collaborative group. CAST: Randomized placebo controlled trial of early aspirin use in 20000 patients with acute stroke. Lancet 1997;349:1641-9.
6. Langhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? Lancet 1993;342:395-8.
7. Vahedi K, Hofmeijer J, Juelttler E, Vica E, George B, Algra A, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: A pooled analysis of three randomized controlled trials. Lancet Neurol 2007;6:215-22.
8. Ingall TO, Fallon W, Louis T, et al. Initial findings of the rt-PA acute stroke treatment review panel. Cerebrovasc Dis 2003;16:S125.
9. DelZappo 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: Prolong in Acute Cerebral Thromboembolism. Stroke 1998;1:4-11.
10. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768-74.
11. Wardlaw JM, Seymour J, Cairns J, Keir S, Lewis S, Sandercok P, Immediate computed tomography scanning of acute stroke is cost effective and improves quality of life. Stroke 2004;35:2477-83.
12. Chen ZM, Sandercok P, Pan HC, Counsell C, Collins R, Liu LS, et al. Indications for early aspirin use in acute ischemic stroke: A combined analysis of 40,000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. Stroke 2000;31:1240-9.
13. Fiebach JB, Schellinger PD, Jansen O, Meyer M, Wilde P, Bender J, et al. CT and diffusion-weighted MR imaging in randomized order: Diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyper acute ischemic stroke. Stroke 2002;33:2206-10.
14. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, et al. Magnetic resonance imaging and computed tomography in emergency assessment in patients with suspected acute stroke: A prospective comparison. Lancet 2007;369:293-8.
15. Wardlaw JM, Keir SL, Seymour J, et al. What is the best imaging strategy for acute stroke? Health Technol Assess 2004;8:14-5.
16. Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: Results from an international collaboration. Stroke 1997;28:491-9.
17. Bamford J, Sandercok P, Dennis M, Burn J, Warlow CP. A prospective study of acute cerebrovascular disease in the community: The Oxfordshire Community Stroke Project 1981-86. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid hemorrhage. J Neurol Neurosurg Psychiatry 1990;53:16-22.
18. Handschu R, Garling A, Heuschmann PU, Kolominsky-Rabas PL, Erbguth F, Neundörfer B. Acute stroke management in the local general hospital. Stroke 2001;32:866-70.
19. Wardlaw JM, Keir SL, Dennis M. The impact of delays in computed tomography of the brain on the accuracy of diagnosis and subsequent management in patients with minor strokes. J Neurol Neurosurg Psychiatry 2003;74:77-81.
20. Bamford J, Sandercok P, Dennis M, Warlow C, Jones L, Mcpherson K, et al. A prospective study of acute cerebrovascular disease in the community: The Oxfordshire Community Stroke Project 1981-86 1, Methodology, demography and incident cases of first ever strokes. J Neurol Neurosurg Psychiatry 1988;51:1373-80.
21. von Kummer R, Meyding-Lamade U, Forstling M, Rosin L, Rieke K, Hacke W, et al. Sensitivity and prognostic value of early CT in occlusion of middle cerebral artery trunk. AJNR Am J Neuroradiol 1994;15:9-15.
22. Barber PA, Demchuk AM, Hudon ME, Pexman JH, Hill MD, Buchan AM. Hyper dense sylvian fissure MCA "dot sign": A CT marker of acute ischemia. Stroke 2001;32:84-8.
23. Leary MC, Kidwell CS, Villablanca JP, Starkman S, Jahan R, Duckwiler GR, et al. Validation of computed tomography middle cerebral artery "dot sign": An angiographic correlation study. Stroke 2003;34:2636-40.
24. Truwit CL, Barkovich AJ, Gean Marton A, Hibri N, Norman D. Loss of the insular ribbon: Another early CT sign of acute middle cerebral artery infarction. Radiology 1990;176:801-6.
25. Marks MP, Holmgren EB, Fox AJ, Patel S, von Kummer R, Froehlich J. Evaluation of early computed tomographic findings in acute ischemic stroke. Stroke 1999;30:389-92.
26. Wardlaw JM, Farall AJ. Diagnosis of stroke on neuro imaging. BMJ 2004;328:655-6.
Dhamija, et al. Neuroimaging in acute stroke

27. Dzialowski I, WeberJ, Doerfler A, Forsting M, von Kummer R. Brain tissue water uptake after middle cerebral artery occlusion assessed with CT. J Neuroimaging 2004;14:42-8.

28. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intra venous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: The European Cooperative Acute Stroke study (ECASS). JAMA 1995;274:1017-25.

29. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-7.

30. Gilligan AK, Markus R, Read S, Srikanth V, Hirano T, Fitt G, Arndts M, et al. Baseline blood pressure but not early Computed Tomography changes predict major hemorrhage after streptokinase in acute ischemic stroke. Stroke 2002;33:2366-42.

31. Quereshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Janjua N, et al. IV tissue plasminogen activator beneficial in patients with hyper dense artery sign? Neurology 2000;66:1171-4.

32. Tomskick TA, Brot TG, Ollinger CP, Barsan W, Spilker J, Eberle R, et al. Hyper dense middle cerebral artery: Incidence and quantitative significance. Neuroradiology 1989;31:312-5.

33. Patel SC, Levine SR, Tilley BC, Grotta JC, Lu M, Frankel M, et al. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. JAMA 2001;286:2830-8.

34. Grotta JC, Chiu D, Lu M, Patel S, Levine SR, Tilley BC, et al. Agreement and variability in the interpretation of early CT changes in stroke patients qualifying for intravenous rTPA therapy. Stroke 1999;30:1528-33.

35. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al. Use of the Alberta stroke program early CT score (ASPECTS) for assessing CT Scans in patients with acute stroke. Am J Neuroradiol 2001;22:1534-42.

36. Coutts SB, Hill MD, Demchuk AM, Barber PA, Pexman JH, Buchan AM. ASPECTS reading requires training and experience. Stroke 2003;34:e179.

37. Coutts SB, Demchuk AM, Barber PA, Hu WY, Simon JE, Buchan AM, et al. Inter observer variation of ASPECTS in real time. Stroke 2004;35:e103-5.

38. Dzialowski I, Hill MD, Coutts SB, Demchuk AM, Kent DM, Wunderlich O, et al. Extent of early ischemic changes on computed tomography before thrombolysis: Prognostic value of the Alberta Stroke Program Early CT Score in ECASS11. Stroke 2006;37:973-8.

39. Mullins ME, Schaefer PW, Sorenson AG, Halpern EF, Ay H, He J, et al. CT and Conventional and diffusion weighted MR imaging in acute stroke: Study in 691 patients at presentation to the emergency department. Radiology 2002;224:353-60.

40. Adams HP, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furnan A, et al. Guidelines for the early management of adults with ischemic strokes: A guidelines from the AHA/ASA, Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Interventional Council and the Atherosclerotic PVD and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Stroke 2007;38:1655-711.

41. Becker H, Desch H, Hacker H, Pencz A. CT Foggino 867 effect with ischemic cerebral infarcts. Neuroradiology 1979;18:185-92.

42. Sidman R, Connolly E, Lemke T. Subarachnoid hemorrhage diagnosis: Lumbar puncture is still needed when the computed tomography scan is normal. Acad Emerg Med 1996;3:827-31.

43. Masdeu JC, Inemia P, Asenbaum S, Bogousslavsky J, Brainin M, Chabriat H, et al. EFNS guideline on neuroimaging in acute stroke: Report of an EFNS task force. Eur J Neurol 2006;13:1271-83.

44. Virapongse C, Cazenave C, Quisling R, Sarwar M, Hunter S. The brain MRI in acute stroke: Lumbar puncture is still needed when the computed tomography scan is normal. Acad Emerg Med 1996;3:827-31.

45. Blakely DD, Odatee EZ, Hasselblad V, Simel DI, Matchar DB. Non invasive carotid artery testing: A meta-analysis review. Ann Intern Med 1995;122:360-7.

46. Dharmija et al. Neuroimaging in acute stroke.
subtraction angiography in carotid artery stenosis: A systematic review. Stroke 2003;34:1324-32.
69. Chiesa R, Melissano G, Castellano R, et al. Three dimensional time of flight magnetic resonance angiography in carotid artery surgery: A comparison with digital subtraction angiography. Eur J Vasc Endovasc Surg 1993;7:171-6.
70. Saloner D. Preoperative evaluation of carotid artery stenosis: Comparison of contrast enhanced MR angiography and duplex ultrasonography with digital subtraction angiography. AJNR Am J Neuroradiol 2003;24:1034-5.
71. Koellemay MJ, Nederkoorn PJ, Reitsma JB, Majoe CB. Systemic review of combined tomographic angiography for assessment of carotid artery disease. Stroke 2004;35:2306-12.
72. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia-the ischemic penumbra. Stroke 1981;12:723-25.
73. Donnan GA, et al. The Ischemic Penumbra. Informa Healthcare USA Inc; 2007.
74. Muir KW, Buchan A, von Kummer R, Rother J, Baron JC. Imaging of acute stroke. Lancet Neurol 2006;5:755-68.
75. Ly JV, Zavala J, Donnan GA. Neuroprotection and thrombolysis: Combination therapy in acute ischemic stroke. Exp Opin Pharmacother 2006;7:1571-81.
76. Markus R, Reutens DC, Kazui S, Read S, Wright P, Pearce DC, et al. Hypoxic tissue in ischemic stroke: Persistence and clinical consequences of spontaneous survival. Brain 2004;127:1427-36.
77. Davis SM, Donnan GA, Butcher KS, Parsons M. Selection of thrombolytic therapy beyond 3h using magnetic resonance imaging. Curr Opin Neurol 2003;16:47-52.
78. Donnan GA, Davis SM. Neuroimaging the ischemic penumbra and selection of patients for acute stroke therapy. Lancet Neurol 2002;1:417-25.
79. Eastwood JD, Lev MH, Azhari S, Read S, Wright P, Pearce DC, et al. Comparison of admission perfusion computed tomography and qualitative and diffusion weighted magnetic resonance imaging in acute stroke patients. Stroke 2002;33:2025-31.
80. Wintemark M, Reichart M, Cuisenaire O, Maeder P, Thiran JP, Schnyder P, et al. Comparison of admission perfusion computed tomography and qualitative diffusion and perfusion weighted magnetic resonance imaging in acute stroke patients. Stroke 2002;33:2025-31.
81. Koenig M, Kraus M, Theek C, Klotz E, Gehlen W, Heuser L. Patency and perfusion-diffusion mismatch in acute ischemic stroke and its potential clinical use. Arch Neurol 2001;58:1069-74.
82. Kohmann M, Juttler E, Huttner HB, Nowe T, Schelling PD. Acute stroke imaging for thrombolytic therapy: An update. Cerebrovasc Dis 2007;24:161-9.
83. Klyuvtmas M, van Everdingen KJ, Kappelle LJ, Rams LM, Viergever MA, van der Grond J. Prognostic value of perfusion and diffusion-weighted MR imaging in first 3 days of stroke. Eur Radiol 2000;10:1434-41.
84. Mori S, van Zijl PC. Fiber tracking: Principles and strategies: A technical review. NMR Biomed 2002;15:468-80.
85. Behrens TE, Johansen-Berg H, Jbabdi S, Rushworth MF, Woolrich MW. Probabilistic diffusion tractography with multiple fiber orientations: What can we gain? Neuroimage 2007;34:144-55.
86. Tai YF, Piccini P. Applications of positron emission tomography (PET) in neurology. J Neurol Neurosurg Psychiatry 2004;75:669-76.
87. Heiss WD, Kracht LW, Thiel A, Grond M, Pavlik G. Penumbra probability thresholds of cortical flumazenil binding and blood flow predicting tissue outcome in patients with cerebral ischemia. Brain 2001;124:20-9.
88. Read SJ, Hirano T, Abbot DF, Markus R, Sachinidis JI, Tochon-Danguy HJ, et al. The fate of hypoxic tissue on 18F-fluoromisonidazole positron emission tomography after ischemic stroke. Ann Neurol 2000;48:228-35.
89. Heiss WD, Huber M, Fink GR, Herholz K, Pietrzuky U, Wagner R, et al. Progressive derangement of penifarct viable tissue in ischemic stroke. J Cereb Blood Flow Metab 1992;12:193-203.
90. Donnan G, Wright P, Markus R, Phan TG, Reuten D. The ischemic penumbra: The evolution of a concept. In: Davis S, Fisher M, Warach S, editors. Magnetic resonance imaging in stroke. Cambridge: Cambridge University Press; 2003. p. 191-206.
91. Baron JC. Mapping the ischemic penumbra with PET: Implication for acute stroke treatment. Cerebrovasc Dis 1999;9:193-201.
92. Ly JV, Donnan GA, Villemagne VL. Detection of cerebral amyloid deposition using (11)C-PiB PET in patients with probable cerebral amyloid angiopathy. Int Med J 2007;37:A92.
93. Hirano T, Read SJ, Abbott DF, Baird AE. Prediction of final infarct volume within 6 hours of stroke using Single Photon Emission Computed Tomography with technetium-99mhexamethylpropylene amine oxime. Cerebrovasc Dis 2001;11:119-27.
94. Berrouschot J, Barthel H, von Kummer R, Knapp WH, Hesse...
S, Schneider D. 99m technetium-ethyl-cysteinate-dimer single-photon emission CT can predict fatal ischemic brain edema. Stroke 1998;29:2556-62.

110. Alexandrov AV, Masdeu JC, Devous M, Black SE, Grotta JC. Brain single photon emission CT with HMPAO and safety of thrombolytic therapy in acute ischemic stroke: Proceedings of the meeting of the SPECT Safe Thrombolysis Study Collaborators and the members of the Brain Imaging council of the society of Nuclear medicine. Stroke 2001;11:119-27.

111. Barthel H, Hesse S, Dannenberg C, Rössler A, Schneider D, Knapp WH, et al. Prospective value of perfusion and x-ray attenuation imaging with single photon emission computed tomography in acute cerebral ischemia. Stroke 2001;32:1588-97.

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