

Hyperacute stroke imaging: How much is enough?

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This section presents two contrasting opinions regarding topics of current interest in radiology. In this article, we discuss the role of imaging in directing the therapy of hyperacute ischemic stroke. The initial section describes the advantages of using MRI in this clinical setting and the latter section presents arguments in favor of CT.

Point: MRI is recommended in all cases

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Brain tissue is exquisitely vulnerable to ischemia. In the complete absence of blood flow, available energy stores can maintain neuronal activity for only a couple of minutes. However, in the event of an acute ischemic stroke, the ischemia is often incomplete, with the injured areas of the brain continuing to receive blood from uninjured arterial and leptomeningeal collaterals. The result is a central zone of completely infarcted tissue, referred to as the 'core,' surrounded by a peripheral zone of ischemic but salvageable tissue, referred to as the 'penumbra.'^[1]

The aim of thrombolytic therapy in hyperacute ischemic stroke is to salvage the penumbra.

The penumbra is most elegantly demonstrated by MRI perfusion imaging. The infarcted core is seen as an area of restricted diffusion, whereas the penumbra is depicted on MRI perfusion maps as a larger area of elevated mean transit time (MTT) and decreased cerebral blood flow (CBF). The cerebral blood volume (CBV) in the penumbra is usually normal or mildly increased due to active auto-regulation. Ischemia in the penumbra results in cerebral hypoxia which, in turn, causes vasodilatation due to the active auto-regulation. The vasodilatation results in normal or increased CBV in the penumbra. Thus, a mismatch in the abnormalities seen on diffusion-weighted (DWI) images and perfusion maps indicates the presence of a penumbra.

The MRI perfusion study plays a crucial role in the decision to thrombolysis. If there is no mismatch, thrombolysis is not recommended since there is no ischemic tissue to salvage. A large infarct (large diffusion abnormality) with a small penumbra must be treated carefully, taking into consideration the time after ictus, since a large infarct size is related to a greater incidence of post-thrombolysis reperfusion injury. Finally a small infarct (small diffusion abnormality) with a large penumbra is a definite indication for thrombolysis (in the absence of hemorrhage), since it implies the presence of a significant amount of ischemic tissue that can be salvaged by recanalization.

Numerous studies have shown that an untreated or unsuccessfully treated penumbra, depicted on MRI perfusion, demonstrates lesion progression both clinically and on follow-up MRI studies. This means that on follow-up MRI, the diffusion abnormality increases to match the defect seen on the initial MRI perfusion maps, implying infarction of the penumbra as well. On the other hand, successful recanalization following demonstration of a penumbra on MRI, is not associated with lesion progression and the diffusion abnormality remains the same on follow-up imaging. These observations emphasize the accuracy of MRI perfusion in guiding management and in prognostication.

Another advantage of MRI over CT is the larger volume that can be studied with MRI perfusion techniques as compared to CT perfusion. CT perfusion with a four-slice scanner allows merely two slices to be obtained. If an infarct is not demonstrated on plain CT, these two slices are often acquired at the level of the basal ganglia and thus it may not be possible to evaluate ischemia that has occurred at a higher level.

Visually, the depiction of a penumbra is more appealing on MRI than on CT. On CT, a penumbra is demonstrated as a mismatch between CBF and CBV maps. This may be

difficult for a clinician to interpret and often requires the expertise of a trained diagnostic radiologist. On the other hand, a diffusion–perfusion mismatch on MRI can be easily appreciated by a clinician with little or no training in diagnostic radiology.

The goals of imaging in acute ischemic stroke are the assessment of the four 'P's, i.e., parenchyma, pipes (blood vessels), perfusion, and penumbra.^[2] Besides studying cerebral perfusion, the primary aim of imaging is to establish the diagnosis of stroke and to rule out stroke mimics such as tumor, as well as to rule out hemorrhage, which is an absolute contraindication for thrombolysis. Newer MRI susceptibility sequences are as sensitive as CT for the depiction of hemorrhage in an acute infarct.

In future, the selection of patients for thrombolytic therapy may be made more effective by performing appropriate imaging studies such as MRI rather than relying on the time of onset as the sole determinant of selection.^[1] In a recent trial,^[3] intravenous desmoteplase injection at 3–9 h after onset was associated with a higher rate of reperfusion and better clinical outcome in patients selected because of a mismatch between the findings of diffusion and perfusion MRI images. The symptomatic intracranial hemorrhage rate was also low.

A recent study by Kassner *et al.*^[4] advocates the use of MRI permeability imaging in the prediction of subsequent hemorrhage in acute ischemic stroke. Increased risk of hemorrhagic transformation limits the use of tissue plasminogen activator (tPA) for thrombolytic treatment. MRI permeability imaging is an emerging technique that is based on dynamic contrast-enhanced imaging and subsequent kinetic modeling of microvascular permeability that allows for quantification of the defects in the blood–brain barrier (BBB). In their study, the authors found significantly increased permeability in three patients of acute ischemic stroke, all of whom hemorrhaged later. They concluded that MRI permeability offers the potential

for identifying patients at increased risk for hemorrhagic transformation. Thus, in the future, physiologic MRI imaging rather than time from onset of symptoms will guide treatment decisions.

The availability of magnets in our country is increasing and MRI facilities are usually available in centers where thrombolysis is offered. A complete MRI study, including T2W or fluid-attenuated inversion recovery (FLAIR) images, a susceptibility sequence (to rule out hemorrhage), diffusion and perfusion images, and MRI angiography, provides comprehensive information to the interventional neuroradiologist and neurologist in order to plan treatment. The entire protocol can be performed in 15 min. Hence, an MRI study is recommended as the first-line investigation for hyperacute ischemic stroke.

The following case demonstrates the ability of MRI to accurately depict the penumbra and direct the decision to thrombolysis:

A 55-year-old man was sent for an MRI study [Figure 1] 2 h after the onset of an acute right hemiparesis. T2W images (Figure 1A) were normal. The DWI image (Figure 1B) showed a small hyperacute infarct in the left MCA territory. The gradient image (Figure 1C) showed no hemorrhage in the infarct. The MTT map (Figure 1D) of the perfusion study showed a significantly large penumbra, depicted as an area of increased MTT, which is much larger than the area of restricted diffusion. The MRI angiogram (Figure 1E) showed occlusion of the left MCA. In view of the presentation within the 3 h window period, the small size of the infarct, the absence of hemorrhage, and the presence of a large penumbra, this patient was considered an excellent candidate for thrombolysis. Unfortunately, the patient's family refused thrombolytic therapy.

Follow-up MRI 7 days later [Figure 2] showed that the penumbra had infarcted. A large infarct was now visible on the T2W image (Figure 2A). The area of restricted diffusion (Figure 2B), depicting the infarct, had now progressed

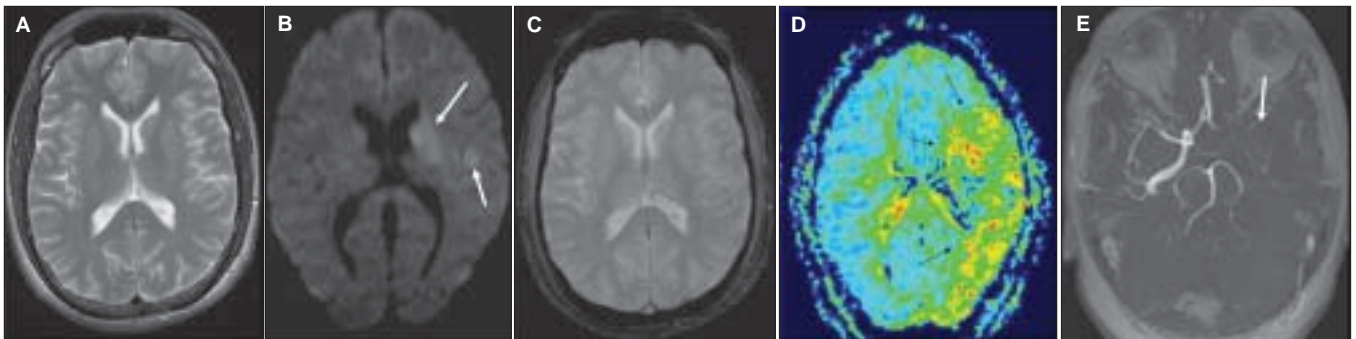


Figure 1 (A-E): Acute stroke. MRI: The T2W image (A) is normal. The DWI image (B) shows a small hyperacute infarct in the left MCA territory (arrow). The gradient image (C) shows no hemorrhage in the infarct. The mean transit time (MTT) map (D) of the perfusion study shows a significantly large penumbra, depicted as an area of increased MTT (arrows), which is much larger than the area of restricted diffusion. The MRI angiogram (1E) shows occlusion of the left MCA (arrow)

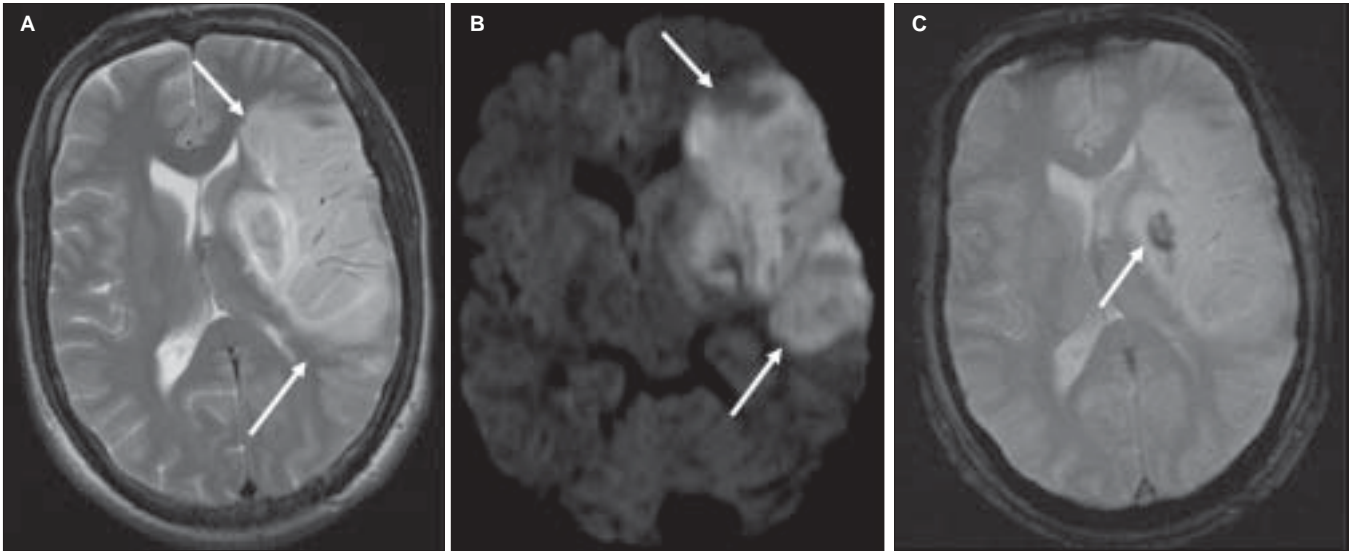


Figure 2 (A-C): Follow-up MRI of patient depicted in Figure 1. The T2W axial image (A) shows a large infarct (arrows). The DWI image (B) shows that the area of restricted diffusion (arrows) has now progressed to match the size of the MTT abnormality in Figure 1D. The gradient image (C) shows mild hemorrhagic transformation (arrow) of the infarct

to match the size of the MTT abnormality on the initial perfusion study. This meant that the untreated penumbra had infarcted. Clinically, the power had decreased from the time of initial presentation 1 week earlier and the patient was hemiplegic. The gradient image (Figure 2C) showed mild hemorrhagic transformation of the infarct.

Counterpoint: CT is an appropriate first-line investigation

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Stroke is the 3rd leading cause of death and the foremost cause of morbidity all over the world. It is well known that if acute ischemic stroke is not reversed, it may lead to devastating consequences. Acute stroke therapy has developed over the last few years and is now available in many centers across India.

The management of acute ischemic stroke involves cerebrovascular recanalization with thrombolytic agents (rt-PA or urokinase) or mechanical devices (Merci device). The former treatment can be given by the intravenous or intraarterial routes and the latter via endovascular means. The aim of acute ischemic stroke therapy is to salvage the penumbra. The penumbra is a nonfunctional, but noninfarcted, territory of brain parenchyma which, if reperfused, can significantly decrease mortality and morbidity.^[5-13]

Emergency neuroimaging is required prior to therapy in order to rule out a bleed, a large infarction, and other causes such as tumor, infection, etc., which are stroke mimics. Brain CT is able to provide the essential basic information

required for thrombolytic therapy. Newer generation CT scanners give us the necessary detail required to decide on the fitness of a patient for thrombolytic therapy. All trials done so far for intravenous and intraarterial thrombolytic therapy have been based on plain CT images.^[14-16]

The inherent advantage of MRI is that multiplanar sequence imaging can be performed and a series of specialty sequences can be obtained, which provide detailed information about the status of the ischemic zone. However, these sequences are time consuming. Also, MRI imaging is almost always performed after a preliminary CT scan. The MRI stroke protocol (DWI and ADC mapping) can detect ischemic brain tissue within minutes of onset. MRI perfusion studies along with DWI help us demarcate the salvageable penumbra. If the diffusion-perfusion mismatch is more than 20%, these patients are candidates for revascularization therapy. MRA helps us screen the vascular tree and localize large vessel occlusion. To have an ideal MRI-based protocol, we should have an MRI exclusively for the stroke service, near the emergency room, so that it can be utilized as the primary imaging modality.^[17-23] This is not always the case in our country.

With advances in imaging techniques and better availability, there is an increasing tendency for clinicians to perform every possible imaging test for acute ischemic stroke, without assessing its clinical significance in the practice of stroke management. While acknowledging these advances and their efficacy, we should not forget that we have a patient to treat and that, with prompt treatment, there is every chance that he/she could recover well.

'Time is brain!' We should not forget that time is always short and in our zest to get that additional bit of information,



Figure 3 (A-C): Acute stroke. CT scan: Axial CT image (A) is normal. The catheter angiogram (B) shows occlusion of the inferior division of the right MCA (arrow), along with occlusion of the contralateral ICA. Repeat angiogram (C), after revascularization, shows that the occluded MCA branch has now recanalized (arrow)

which really at times is useless, we lose valuable time within the therapeutic window.

We practice intraarterial thrombolysis with rt-PA in the first 6 h of an acute ischemic stroke. In our stroke protocol, all patients with a significant neurological deficit within the first 3 h of onset are subjected to a CT brain. Patients with a normal CT study are subjected to intraarterial thrombolysis with rt-PA without any other imaging investigations. We consider MRI only in patients who present after 3 h or when the CT scan findings are equivocal (loss of grey–white differentiation, infarction involving more than 1/3rd of cortical arterial territory), prior to shifting them to the digital subtraction angiography (DSA) lab.

There is considerable difference of opinion between clinicians and institutes regarding the practice of acute stroke therapy. Every effort should be made to formalize a practical and efficient imaging protocol for acute stroke and to make it ‘patient-centric.’ We suggest that once the protocol is formed, it should be adhered to for a reasonable time period, so that its efficacy and practicality can be assessed.

To conclude, CT imaging has proven to be an effective and accurate first-line investigation for acute ischemic stroke. It is widely available and time tested. Its greatest advantage is its speed, since time is of crucial importance in the management of acute ischemic stroke. A plain CT study of the brain can be acquired in a minute on modern multi-slice scanners. Unlike MRI, motion artifacts are not a problem. A CT perfusion study and angiogram may be added in select cases. CT is exquisitely sensitive to hemorrhage, the demonstration of which is a contraindication for thrombolysis. CT studies are easy to interpret in acute settings. Finally, all major studies of acute stroke therapy (NINDS, ECASS, PROACT) have used CT for imaging. Hence, data regarding CT in this clinical setting is more

robust and reliable for direct management.

The following case illustrates the utility of CT imaging in the management of patients with acute ischemic stroke:

A 69-year-old man presented with left hemiplegia and aphasia of 3 h duration. His CT study of the brain was normal [Figure 3A]. The patient was shifted to the DSA suite without any further imaging. On angiogram, he was detected to have occlusion of the inferior division of the right middle cerebral artery (MCA) [Figure 3B]. The contralateral internal carotid artery (ICA) was occluded. A microcatheter over a neuro microwire was navigated into the occluded segment and revascularization was achieved after infusion of 40 mg of rt-PA [Figure 3C]. The patient on admission had a National Institute of Health (NIH) stroke scale of 22, which reduced to 8 at 24 h and to 3 at 1 week. The patient had an MRS of 1 on discharge at seven days.

References

1. Srinivasa A, Goyal M, Al Azri F, Lum C. State-of-the-art imaging of acute stroke. *Radiographics* 2006;26:S75-95.
2. Rowley HA. The four Ps of acute stroke imaging: Parenchyma, pipes, perfusion and penumbra. *AJNR Am J Neuroradiol* 2001;22:599-601.
3. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, *et al.* The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): A phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005;36:66-73.
4. Kassner A, Roberts T, Taylor K, Silver F, Mikulis D. Prediction of hemorrhage in acute ischemic stroke using permeability MRI imaging. *AJNR Am J Neuroradiol* 2005;26:2213-7.
5. 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.
6. Schmuelling S, Grond M, Rudolf J, Heiss WD. One-year follow-up in acute stroke patients treated with rtPA in clinical routine. *Stroke* 2000;31:1552-4.
7. 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;282:2003-11.
8. Gonner F, Remonda L, Mattle H, Sturzenegger M, Ozdoba C, Lovblad KO, *et al.* Local intra-arterial thrombolysis in acute stroke. *Stroke* 1998;29:1894-900.
 9. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, *et al.* Randomized double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 1998;352:1245-51.
 10. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M, *et al.* 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;29:4-11.
 11. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset: The ATLANTIS study: A randomized controlled trial: Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA* 1999;282:2019-26.
 12. Warach S. New imaging strategies for patient selection for thrombolytic and neuroprotective therapies. *Neurology* 2001;57: S48-52.
 13. Lovblad KO, Baird AE. Actual diagnostic approach to the acute stroke patient. *Eur Radiol* 2006;16:1253-69.
 14. Ernst R, Pancioli A, Tomsick T, Kissela B, Woo D, Kanter D, *et al.* Combined intravenous and intra-arterial recombinant tissue plasminogen activator in acute ischemic stroke. *Stroke* 2000;31:2552-7.
 15. Padma MV, Singh MB, Bhatia R, Srivastava A, Tripathi M, Shukla G, *et al.* Hyperacute thrombolysis with IV rtPA of acute ischemic stroke: Efficacy and safety profile of 54 patients at a tertiary referral center in a developing country. *Neurol India* 2007;55:46-9.
 16. von Kummer R, Allen KL, Holle R, Bozzao L, Bastianello S, Manelfe C, *et al.* Acute stroke: Usefulness of early CT findings before thrombolytic therapy. *Radiology* 1997;205:327-33.
 17. Lin DD, Filippi CG, Steever AB, Zimmerman RD. Detection of intracranial hemorrhage: Comparison between gradient-echo images and b images obtained from diffusion-weighted echoplanar sequences. *AJNR Am J Neuroradiol* 2001;22:1275-81.
 18. Grand S, Lefournier V, Krainik A, Bessou P, Tropres I, Chabardes S, *et al.* MR and CT perfusion imaging of the brain: principles and clinical applications. *J Radiol* 2007;88:444-71.
 19. Srinivasan A, Goyal M, Al Azri F, Lum C. State-of-the-art imaging of acute stroke. *Radiographics* 2006;26:S75-95.
 20. Wintermark M, Fiebach J. Iodinated and gadolinium contrast media in computed tomography (CT) and magnetic resonance (MRI) stroke imaging. *Curr Med Chem* 2006;13:2717-23.
 21. Schaefer PW, Copen WA, Lev MH, Gonzalez RG. Diffusion-weighted imaging in acute stroke. *Magn Reson Imaging Clin N Am* 2006;14:141-68.
 22. Lauzon ML, Sevick RJ, Demchuk AM, Frayne R. Stroke imaging at 3.0 T. *Neuroimaging Clin N Am* 2006;16:343-66.
 23. Arakawa S, Wright PM, Koga M, Phan TG, Reutens DC, Lim I, *et al.* Ischemic thresholds for gray and white matter: A diffusion and perfusion magnetic resonance study. *Stroke* 2006;37:1211-6.

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