Application of acute stroke imaging

Selecting patients for revascularization therapy

Tiesong Shang, MD, PhD
Dileep R. Yavagal, MD

Correspondence & reprint requests to Dr. Yavagal: dyavagal@med.miami.edu

ABSTRACT

Due to the dynamic and versatile characteristics of ischemic penumbra, selecting the right acute ischemic stroke (AIS) patients for revascularization therapy (RT) based on initial available imaging can be challenging. The main patient selection criterion for RT is the size of the mismatch between the potentially salvageable tissue (penumbra) and the irreversibly damaged tissue (core). The goal of revascularization RT is to "freeze" the core and prevent it from extending to the penumbral tissue. Penumbral imaging selection of AIS patients for RT, using magnetic resonance or CT-based studies, may provide more clinical benefit to the appropriate patients, although direct evidence is pending. Not all penumbra-core mismatches beyond 3 hours are equal and need treatment, and defining which mismatches to target for RT is the current goal of ongoing clinical trials. In addition to "penumbral"-based imaging, large vessel occlusion and clot length estimation based on CT angiography and noncontrasted ultrathin CT scan has been used to identify patients who are refractory to systemic thrombolysis and may be eligible for endovascular therapy. The application of various imaging modalities in selecting and triaging AIS patients for RT is discussed in this review. Larger prospective randomized trials are needed to better understand the role of various imaging modalities in selecting AIS patients for RT and to understand its influence on clinical outcome. ***Neurology*® 2012;79 (Suppl 1):S86–S94**

GLOSSARY

AIS = acute ischemic stroke; **BBB**= blood–brain barrier; **CBF** = cerebral blood flow; **CBV** = cerebral blood volume; **CTA** = CT angiography; **CTP** = CT perfusion; **DWI** = diffusion-weighted imaging; **ET** = endovascular therapy; **ICM** = imaging-clinical mismatch; **MCA** = middle cerebral artery; **MERCI** = Mechanical Embolus Removal in Cerebral Ischemia; **MRA** = magnetic resonance angiography; **MRP** = magnetic resonance perfusion; **mRS** = modified Rankin Scale; **MTT** = mean transit time; **NCCT** = noncontrasted CT; **PWI** = perfusion-weighted imaging; **rtPA** = recombinant tissue plasminogen activator; **sICH** = symptomatic intracranial hemorrhage; **SVIN** = Society of Vascular and Interventional Neurology; **THERAPY Trial** = Assess the Penumbra System in the Treatment of Acute Stroke trial; **T-max** = time to maximum.

Although acute ischemic stroke (AIS) is the leading cause of disability worldwide, treatment options for AIS remain limited to systemic and local revascularization therapies. Currently, the only US Food and Drug Administration–approved treatment for AIS is IV recombinant tissue plasminogen activator (rtPA), which must be administered within 3 hours of symptom onset.[1] Results from the ECASS III trial have since expanded treatment to 4.5 hours; however, the majority of AIS patients still do not receive IV rtPA because of this narrow time window.[2] Endovascular therapy (ET) may be considered for AIS patients for whom IV rtPA fails, who do not qualify for IV rtPA treatment, or who present beyond the IV rtPA time window. Despite the relatively high reported recanalization rate of ET (48% to 87%), good clinical outcome is limited to 25% to 41%.[3–9] One possible explanation of the discrepancy between recanalization and clinical outcome rates is the presence of variable sizes of salvageable brain tissue (penumbra) in the ischemic territory. Penumbra-based imaging, large-vessel occlusion, and clot length estimation based on CT angiography (CTA) and ultrathin noncontrasted CT (NCCT) head scanning have been used to identify patients who are refractory to systemic thrombolysis and may be appropriate for ET, thus potentially improving clinical outcome. Selecting patients on the basis of vessel occlusion and clot length is the main target for an ongoing clinical trial,

From the Departments of Neurology (T.S., D.R.Y.) and Neurosurgery (D.R.Y.), University of Miami, Miami, FL.
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Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY trial).[10] The THERAPY trial is based on an AIS study that found limited response to systemic thrombolysis in patients with a clot length of ≥8 mm identified on an ultrathin NCCT head scan.[11]

Establishing the best AIS imaging protocol, whether CT- or MRI-based, to identify salvageable tissue, vessel occlusion, and clot length prior to interventional treatment may be useful in avoiding futile therapy and improving clinical outcome. However, AIS pretreatment imaging needs to fulfill certain prerequisites, including providing reliable and consistent results, ultrafast acquisition and postprocessing, and 24/7 availability, prior to its wide application in future trials and routine adaptation in daily clinical practice.

In this article, which is based on a presentation during the Society of Vascular and Interventional Neurology (SVIN) roundtable meeting and is presented here as a complementary part of the imaging section of this supplement, we present an overview of the application of various imaging modalities in selecting and triaging AIS patients for ET. Additional discussion is found in the editorial and accompanying articles in this imaging section.

THE CONCEPT OF PENUMBRA

The concept of penumbra was first described in the late 1970s to early 1980s.[12,13] The penumbra is an area of vulnerable brain tissue that surrounds the central area of an infarct core. In the central core of infarction, irreversible tissue damage occurs when cerebral blood volume (CBV) decreases dramatically and cells die rapidly. However, in the penumbra, the injury is thought to be reversible as cerebral blood flow (CBF) is reduced to a critical point where the cells are dysfunctional and possibly "stunned." This area has some energy to maintain membrane potential but not enough to perform physiologic function. Without effective treatment, cell death occurs and the penumbra will be recruited into the infarct core. Penumbra is estimated to be present in up to 80% of AIS patients.[12,13] The duration of penumbra is variable, with studies reporting time ranges of 6 to 24 hours after symptom onset.[12,13] "Core freeze" and "penumbra reperfusion" are the main targets of AIS therapeutic intervention. Identifying the extent of the penumbra and tailoring therapeutic options accordingly might aid in avoiding unnecessary therapy and complications and may potentially improve clinical outcome.

Imaging identification of penumbra. CT without contrast is used in AIS patients to rule out hemorrhage, large ischemic infarct, and other underlying pathology that contraindicates IV rtPA treatment; however, it may provide only limited information regarding the penumbra. Advanced neuroimaging could provide a more comprehensive survey of real-time pathophysiology of AIS, with accurate identification of the site of arterial occlusion, evaluation of hemodynamic and pathophysiologic impact on the brain parenchyma, and identification of the penumbra. These imaging techniques include magnetic resonance angiogram (MRA), magnetic resonance perfusion (MRP), CTA, and CT perfusion (CTP).[14–20] The penumbra is defined for clinical and practical purposes as the mismatch between the infarct core and hypoperfused region, which can be appreciated on diffusion-weighted imaging (DWI) and perfusion-weighted (PWI) MRI, respectively.[14–18] On CTP, the infarct core correlates with CBV and CBF, and the hypoperfused area (penumbra) correlates with CBF, time to maximum (T-max), and mean transit time (MTT) values.[18–20] The penumbra is the region of difference between these presumed areas of core infarct and hypo/slow perfusion. MRP and CTP have relatively good correlation in identifying the penumbra.[20] Using either imaging modality (CTP or MRP) to triage AIS patients for ET beyond the traditional time window appears to be a safe and feasible approach.[21] In a multicenter registry that applied either magnetic resonance or CT penumbral imaging triage in 237 AIS patients treated with ET who presented beyond 8 hours of symptoms onset, 73.84% had successful revascularization, with an 8.86% symptomatic intracranial hemorrhage (sICH) rate. The 3-month mortality rate was 21.5%, and good clinical outcomes (modified Rankin Scale [mRS] score of 2 or less) were seen in 45% of patients.[21]

In the subsequent sections, we summarize a proposed CT- and MRI-based AIS imaging triage protocol for revascularization therapy.

CT PERFUSION PROTOCOL

CTP was initially described in AIS in 1980.[22] The technology, software, and image resolution of CTP have evolved in the past 2 decades to allow its wide application in clinical practice. CTP estimates the contrast growth and decay (increase and decrease in tissue attenuation) over time as it passes initially through the brain tissue. The linear relationship between the contrast

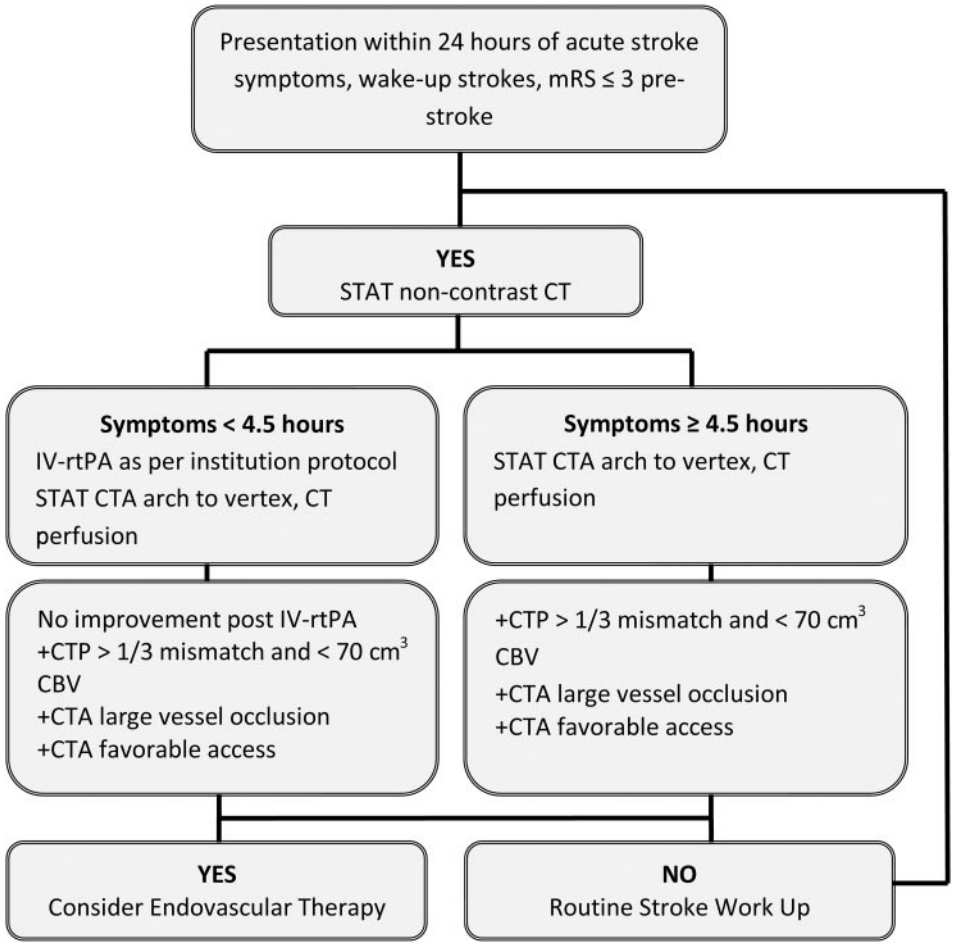
concentration and resolution from the tissue allows the CT software to create time-vs-contrast concentration curves. This is determined by inputting manually or automatically standard arterial and venous regions of interest, such as the anterior cerebral artery and the torcular herophili.[23]

MTT is defined as the time it takes the contrast to flow through arterial to venous regions in seconds, whereas CBV is the total volume of blood in a region of brain (mL of blood per 100 g of brain tissue). CBF is defined as the volume of blood that passes through a volume of brain tissue over time and is a calculated number of CBV over time (MTT).[23] The mismatch between CBV, CBF, and MTT may be used to estimate the core and penumbra. The penumbra may be identified as MTT − CBV or (1 − CBV/MTT).[18–20,22,23]

CTP has value in identifying significant penumbra-core mismatch and in predicting clinical outcome on the basis of the core infarct volume. In 1 study, none of the patients presenting with AIS with a CTP infarct core volume of >100 mL had a good clinical outcome (as defined by an mRS score ≤2) despite ET to the occluded middle cerebral artery (MCA).[24] In addition to a large-volume infarct seen on CTP predicting the lack of clinical response to ET, CTP seems to predict the prognosis of ischemia seen on the admission CTP scan when compared to the infarct volume on DWI. Among 22 AIS patients treated with ET, for patients whose recanalization failed, the final infarct volume on DWI correlated with the total volume on the initial CTP scan CBV map, whereas those whose recanalization was successful had a smaller final infarct volume on DWI than the initial CBV map.[25]

In a study of 99 consecutive patients with anterior circulation AIS who had undergone ET with preintervention CTP, the rates of recanalization and clinical outcomes were compared with the Mechanical Embolus Removal in Cerebral Ischemia (MERCI), Multi-MERCI, and Penumbra trials.[26] Successfully recanalized patients had a significantly higher rate of good outcome: 67% vs 46% in MERCI, 49% in

Figure 1 **Suggested CT-based imaging triage protocol for endovascular acute ischemic stroke therapy**



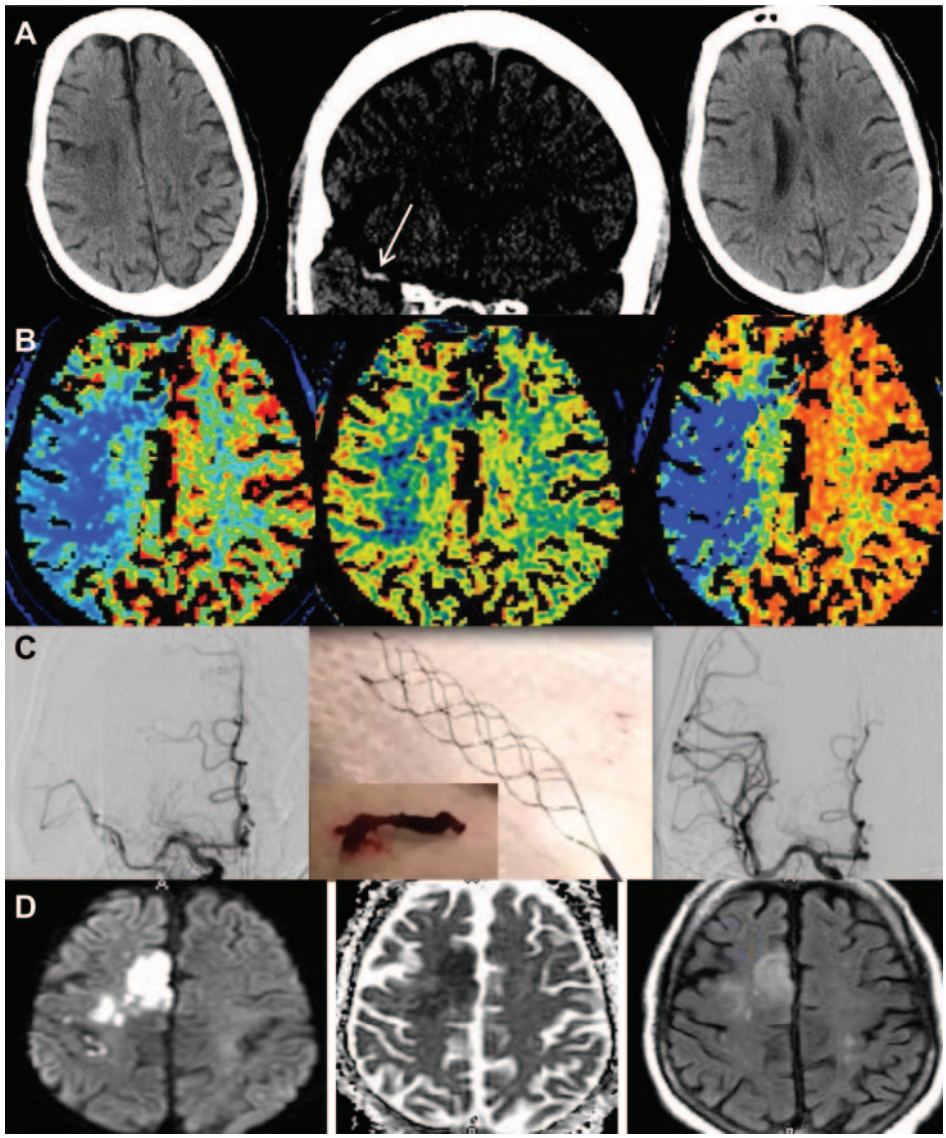
This is a proposed algorithm; hospitals may implement all or parts of this protocol as it applies to their practice pattern and available resources. Abbreviations: CBV = cerebral blood volume; CTA = CT angiography; CTP = CT perfusion; mRS = modified Rankin Scale; rtPA = recombinant tissue plasminogen activator.

Multi-MERCI, and 29% in Penumbra. The rate of futile recanalization was 33%, compared with 54% for MERCI, 51% for Multi-MERCI, and 71% for Penumbra. A small CBV abnormality ($p < 0.0001$) and large MTT-CBV mismatch ($p < 0.0001$) were strong predictors of a good clinical outcome (mRS score ≤ 2).[26]

Although retrospective studies and case series may support the use of CTP, there are limited prospective data on the use of CTP in identifying significant mismatch to triage AIS patients prior to ET in randomized clinical trials. Other limitations of CTP include the coverage area and tissue sampling by CTP, which is usually not sufficient to cover all ischemic regions; the lack of standardized optimal processing; and variations in software, which may produce different CBV, CBF, and MTT maps.[27]

Despite these limitations, the advantages of CTP-based AIS triage are its wide availability (24/7), ultrafast acquisition and processing, and rapid interpretation. The CTP protocol appears to be safe, and there are no differences in the risk of acute nephropathy in hospitalized patients who did or did not receive AIS CT protocol, including those who are followed by conventional angiography.[28] CT ra-

Figure 2 **An example of applying the CT protocol to triage patients with acute ischemic stroke for endovascular therapy**



Row A: baseline noncontrasted CT (sides) showing small area of decreased attenuation on the right side, with right middle cerebral artery 9-mm clot on the coronal ultrathin noncontrasted CT (middle). Row B: CT perfusion blood flow, with mismatch between the cerebral blood flow (left side) or mean transit time (right side) and cerebral blood volume (middle). Row C: anteroposterior cerebral angiogram before (left side) and after clot removal (right side) by means of a Solitaire stent-retriever with 1 pass (middle). Row D: the final infarct on the diffusion-weighted imaging/apparent diffusion coefficient and fluid-attenuated inversion recovery MRI. (This case is courtesy of Dr. O.O. Zaidat.)

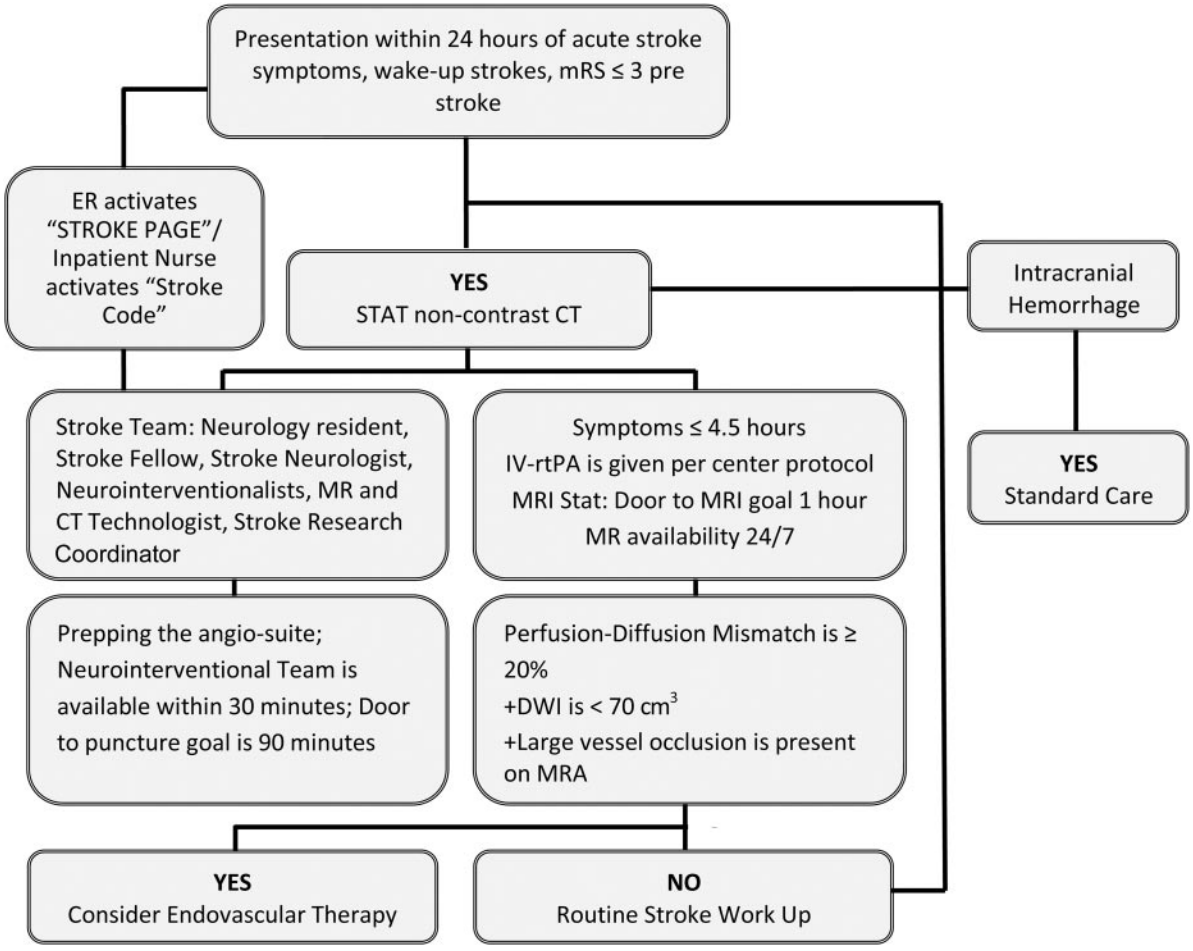
diation dose and safety concerns are balanced, given the benefit of potentially better guidance for ET.[29]

The data obtained from CT-based AIS triage protocol (structural, vascular, and physiologic) imaging are particularly valuable when there is an unquestionably large area of mismatch or large area of infarct volume.

The CT-based AIS triage protocol algorithm, proposed in figure 1, is a suggested outline that can be modified by different institutions according to their available resources. AIS patient CT scan triage by care providers should take the utmost precedence, given the futility of delayed intervention and narrow therapeutic margin when performed for small areas of mismatch or large infarct volume. The CT and MRI radiology technologists are an instrumental part of the stroke team. Hospitals should have technologists trained and geared toward the concept of high-urgency AIS imaging triage for emergency performance and processing of CT imaging. In this proposed protocol (figure 1), patients who present within 24 hours of stroke symptoms onset are evaluated with NCCT, CTA from the arch to the vertex, and CTP. Rapid CT imaging, postprocessing with maximum-intensity projection, multiplanar reformations, and CTP maps need to be in place as part of the routine AIS protocol. If the patient has significant mismatch on CTP and large-vessel occlusion on CTA without clinical improvement or large infarct volume, then ET may be considered (figure 1).

In figure 2, we present an example of a patient who was triaged with a CTP-based protocol. The patient presented with left hemiplegia, drowsiness, and gaze deviation to the left at 5 hours after symptom onset. A CT scan showed a small cortical stroke with a 9-mm right MCA clot. The CTP shows a

Figure 3 **Suggested acute ischemic stroke triage MRI-based protocol**



A "Stat MRI" acute ischemic stroke protocol for endovascular therapy, comprising diffusion-weighted imaging, perfusion-weighted imaging, fluid-attenuated inversion recovery, gradient recalled echo, magnetic resonance angiography, and Circle of Willis. Real-time processing of the perfusion data are done on proprietary software from Phillips to generate time to peak (TTP) gray-scale maps. Perfusion deficit is estimated visually as area of delayed TTP compared with the nonaffected side. Presence of perfusion-diffusion mismatch or imaging-clinical mismatch associated with large-artery occlusion (internal carotid artery, M1 and M2 segments of middle cerebral artery, vertebral artery, basilar artery, P1 segment of posterior cerebral artery) was used as a triaging guideline to offer endovascular therapy. Abbreviations: DWI = diffusion-weighted imaging; MR = magnetic resonance; MRA = magnetic resonance angiography; mRS = modified Rankin Scale; rtPA = recombinant tissue plasminogen activator.

significant area of mismatch between the CBV and MTT or CBF. The angiogram demonstrated right M1 occlusion with complete recanalization by means of a Solitaire stent-retriever device (Covidien, CA) after 1 pass. The final infarct volume on MRI scan corresponded to the initial CT scan and CBV.

In summary, the AIS CTP-based protocol appears to be easily applied, safe, and feasible. The limitations to widely adapting CTP are the lack of optimal standardization of the processing, formatting, and variable threshold parameters to different CTP maps.

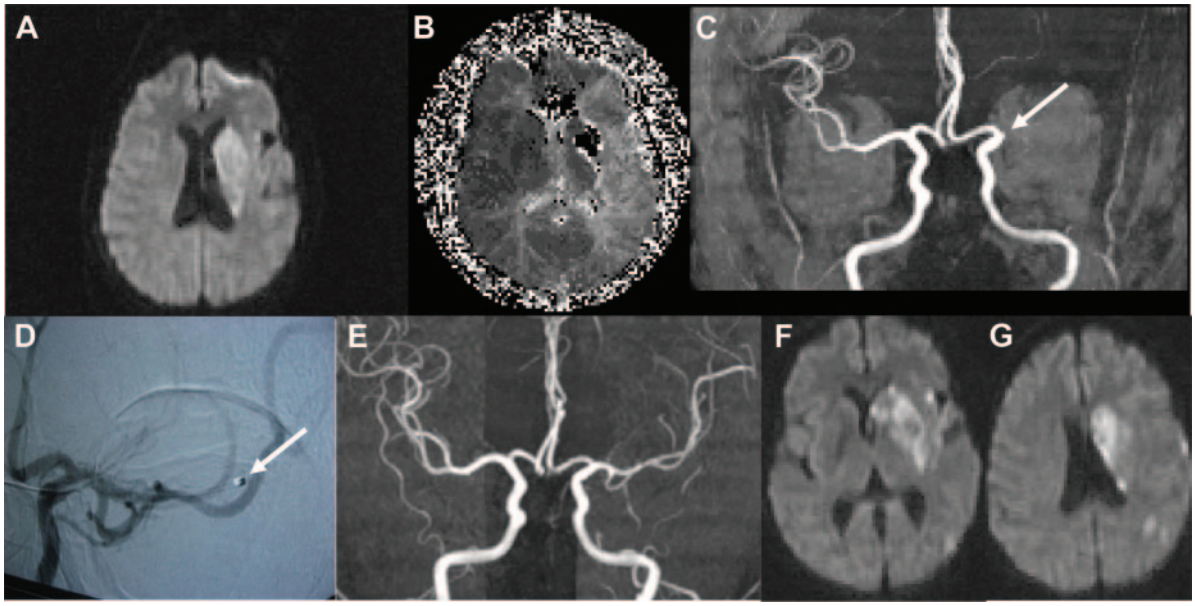
MRI PERFUSION PROTOCOL The approach of using MRI as the basis for selecting AIS patients for reperfusion treatment has been evaluated in several clinical trials.[14–22,30–32] Diffusion-weighted Imaging Evaluation for Understanding Stroke Evolution (DEFUSE), Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET), and Desmoteplase in Acute Ischemic Stroke 2 (DIAS-2) are prospective trials that implemented penumbral imaging in selecting patients for revascularization therapy.[30–32]

The treatable penumbra was identified as a hypoperfused region of at least 20% larger volume than the infarct core; this threshold is considered to have sufficient volume of brain tissue that is at risk and is the target of reperfusion therapy. In the DEFUSE and EPITHET trials, patients were treated with IV rtPA within 6 hours after onset of symptoms. In DIAS-2, patients were randomized by MRP and CTP mismatch criteria and treated with desmoteplase within 9 hours after symptom onset. A meta-analysis of these trials showed improved recanalization/reperfusion but demonstrated no significant improvement in clinical outcome with mismatch-based selection.[33] The sICH rate significantly increased after IV rtPA in this meta-analysis.[33] There were several potential explanations for these results. In the DEFUSE and EPITHET trials, the PWI volume was calculated with use of a T-max threshold >2 seconds delay, which may overestimate the penumbra size and include areas of oligemia. It was proposed later that a T-max >6 seconds delay might be more reliable and appropriate in evaluating penumbra.[34] The rate of large-vessel occlusion was 30% in the DIAS-2 trial,[32] which could explain the good clinical outcome in the control group. The hypothesis is that the penumbra without vessel occlusion rarely evolves into an infarction.

Another MRI-based selection strategy is to select AIS patients who have a moderate to severe deficit with limited abnormality on DWI for ET, and imaging-clinical mismatch (ICM). In a small study of 11 patients presenting beyond 8 hours of symptom onset who had ICM and underwent ET, a decrease in the NIH Stroke Scale score >4 points was achieved in 72% of the subjects without sICH.[35]

The added value in MRI triage of AIS is the potential of excluding patients who have stroke mimics

Figure 4 **Patient presenting with acute onset of global aphasia and right hemiparesis**



The NIH Stroke Scale score was 20 at 2 hours from symptom onset. IV recombinant tissue plasminogen activator (rtPA) of 0.6 mg/kg was given at 2.5 hours. MRI brain attack protocol showed perfusion-diffusion mismatch (A and B) and imaging-clinical mismatch at 3.5 hours, with proximal left middle cerebral artery M1 occlusion (C, arrow). Endovascular therapy was started at 4.0 hours. Proximal M1 was opened on catheter angiography with use of a Penumbra aspiration device (D, arrow), but distal M1 was noted to have persistent occlusion. Intra-arterial rtPA of 12 mg was then injected directly into the thrombus in distal left M1 segment. The patient started to speak and weakly moved right side. The final recanalization and infarct volume in repeat diffusion MRI is shown in E, F, and G. The patient was discharged on day 7 with an NIH Stroke Scale score of 5.

and do not need ET. Stroke mimics were reported to be 3% to 11%.[36] MRI could also exclude patients who are likely to be harmed by revascularization therapy. It is expected that about 10% to 18% of patients with mismatch will be excluded from ET due to the presence of a large DWI lesion on MRI.[37] In a retrospective study of AIS, the diagnosis was changed after MRI in 20 (21%) of 97 patients, and the treatment plan was changed in 25 (26%) of the 97 patients.[16] The MRI data in this study were acquired in less than 15 minutes, a time that is hard to achieve in everyday practice.[16]

In addition to selecting patients who may benefit from ET, MRI-based triage may aid in excluding patients who are at risk for sICH. The rate of sICH in ET trials was 8% to 11%,[3–9] and it was 3.5% to 9.5% in mismatch-guided IV thrombolysis trials.[30–32] The sICH was related to many factors, including age, baseline stroke severity, hyperglycemia, and onset-to-treatment time. As shown in EPITHET and DEFUSE, DWI volume is a very important predictor for sICH. A large infarct volume size, as defined by a DWI >100 mL or PWI >100 mL with a T-max >8 seconds, was considered to be a malignant mismatch.[38] This is approximately greater than one-third the volume of the MCA territory and is found to have a high risk of ICH. Recent studies showed that a DWI lesion volume >70 cm^3 has a high specificity for poor outcome, with or without revascularization therapy.[39] Furthermore, early blood–brain barrier (BBB) disruption in AIS has a propensity for hemorrhage after reperfusion therapy. Detecting BBB permeability by MRP may identify patients who are at risk of hemorrhage.[39, 40] One study using CTP demonstrated that BBB disruption has a sensitivity of 100% and a specificity of 79% for sICH.[41]

The disadvantages of MRI-based protocol include the lack of 24/7 availability, lack of standardization of the software and threshold for postprocessing, and lack of feasibility in patients with metallic implant or claustrophobia. In addition, MRI-based AIS triaging protocol may delay revascularization therapy. In 1 single-center study of 87 consecutive AIS patients undergoing MRI-based protocol for ET triage, the time from MRI order to last MRI was approximately 100 minutes.[42] This time remained unchanged in each consecutive 6-month period following implementation of the MRI selection strategy, indicating that the process to obtain the emergency MRI in AIS patients does not accelerate with increased experience over time.[42] It remains unclear if this added time for MRI is counterbalanced by significant benefit from MRI selection.

However, the sensitivity and specificity of MRI stroke imaging are high, and the information provided on the underlying hemodynamics, pathophysiology, and vasculature are invaluable and can be incorporated into AIS triage protocols in centers where expedited and 24/7 MRI resources are available.

A proposed MRI-based triage protocol for ET in AIS is summarized in figure 3; the suggested protocol involves emergent MRI with DWI, PWI, fluid-attenuated inversion recovery, gradient echo, and MRA of the Circle of Willis in AIS patients who present within 24 hours from symptom onset. The presence of penumbra is determined by PWI-DWI mismatch or ICM. Patients receive IV rtPA prior to ET if qualified. Patients are selected for ET if the mismatch is ≥20% by visual measurement, infarct volume is <70 cm^3, or clinical symptoms are disproportionate to the DWI volume. An example of a case treated with use of this MRI protocol is presented in figure 4.

DISCUSSION AIS patient selection for revascularization therapy using CT-based or MRI-based penumbral and vessel imaging protocols may be useful in avoiding futile therapy and improving clinical outcome. Imaging-based ET clinical trials and standardization of AIS acute imaging/triaging protocols across endovascular centers will further our current understanding of imaging-based patient selection for ET.

AUTHOR CONTRIBUTIONS

Both authors participated in the design, writing, and editing of the final manuscript.

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Tiesong Shang and Dileep R. Yavagal

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