Advanced neuroimaging in acute ischemic stroke: extending the time window for treatment

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Early treatment of ischemic stroke with thrombolytics is associated with improved outcomes, but few stroke patients receive thrombolytic treatment in part due to the 3-hour time window. Advances in neuroimaging may help to aid in the selection of patients who may still benefit from thrombolytic treatment beyond conventional time-based guidelines. In this article the authors review the available literature in support of using advanced neuroimaging to select patients for treatment beyond the 3-hour time window cutoff and explore potential applications and limitations of perfusion imaging in the treatment of acute ischemic stroke. (DOI: 10.3171/2011.3.FOCUS1146)

Key Words • stroke • neuroimaging • thrombolysis • perfusion imaging

Tissue plasminogen activator remains the only FDA-approved treatment for acute ischemic stroke, but only about 2% of patients suffering an ischemic stroke receive tPA, largely because of the rigorous inclusion and exclusion criteria for its use. Among these is the requirement for a 3-hour interval, from onset of symptoms to initiation of therapy. Recent data, however, suggest that the benefits of tPA may extend beyond the 3-hour cutoff. Advanced neuroimaging modalities may help in identifying patients who may still benefit from thrombolytic therapy 3 hours after symptom onset. This review will focus on current imaging modalities used to assess acute ischemic stroke and explore their potential application in patient selection for treatment outside of conventional time-based guidelines.

Thrombolysis in Unselected Patients Using Extended Time Windows

Thrombolysis for acute ischemic stroke in a 0- to 6-hour window was first investigated in large multicenter trials using streptokinase. These trials were halted prematurely when high rates of early fatality and hemorrhage were noted in streptokinase-treated patients. Patients treated with streptokinase after 3 hours were noted to have higher mortality rates than those treated within 3 hours. The use of streptokinase was thus abandoned in favor of rt-PA.

The National Institute of Neurological Disorders and Stroke rt-PA trial was the first trial to establish the efficacy of rt-PA in the treatment of acute ischemic stroke. The trial randomized patients with ischemic stroke into 2 groups (those treated with rt-PA 0–3 hours after stroke onset and those treated with placebo 0–3 hours after stroke onset) and found that rt-PA–treated patients were at least 30% more likely to have mild or no disability on 4 different outcome scales compared with placebo-treated patients. In contrast, the first ECASS failed to show any significant difference in mRS scores or Barthel Index at 90 days using a 0- to 6-hour window between rt-PA– and placebo-treated patients on an intention-to-treat basis. The ECASS II and the subsequent ATLANTIS A and B trials also failed to show any benefit to tPA within 0–6 or 3–5 hours after stroke onset compared with placebo while demonstrating an increased risk of intracerebral hemorrhage. Unlike the streptokinase trials, however, no increase in mortality rate was seen between the 2 groups. A pooled analysis of these trials demonstrated benefit to rt-PA up to 4.5 hours after symptom onset at which point the number needed to treat exceeded the number needed to harm. These findings were confirmed in the recently published ECASS III trial, which
showed a significant benefit to rt-PA treatment within 4.5 hours of ischemic stroke onset despite an increase in intracerebral hemorrhage.

Collectively, the aforementioned data suggest that there may indeed be a point in time at which rt-PA is not only of no clinical benefit but also may have the potential to cause harm. Of note, however, is that the aforementioned trials relied exclusively on clinical impression and noncontrast CT scanning criteria to establish eligibility for treatment. As such, the time windows established in these trials are not based on any physiological basis per se but rather arbitrary cutoff points based on clinical observation. Understanding the pathophysiological changes that occur during ischemic stroke and the ability to observe these changes in real time may be the keys to identifying patients who would derive the most benefit from treatment.

Cerebral Perfusion and the Ischemic Penumbra

Cerebral perfusion refers to tissue blood flow and can be expressed as CBF, CBV, and MTT. Cerebral blood volume is defined as the total volume of blood in a given volume of brain tissue and is described in ml/100 g of brain tissue. Cerebral blood volume is defined as the volume of blood passing through a volume of brain tissue per unit time, and MTT is defined as the average transit time of blood through a given brain region and is measured in seconds. Neuronal dysfunction results after reduction in the CBF below 20 ml/100 g/min. Further reductions in CBF result in failure of the sodium/potassium adenosine triphosphate pump and the ability to maintain the normal cellular osmotic gradient resulting in cellular death. The concept of the ischemic penumbra relates to neuronal tissue that exhibits impaired function but has not progressed to cell death. The ischemic core relates to the latter tissue, which is irreversibly damaged. Without restoration in blood flow, the threshold for the core approaches that of the penumbra, resulting in expansion of the core size. Because both the penumbra and core contribute to clinical symptoms, theoretically the restoration of blood flow to the ischemic penumbra would result in improved clinical function while little would be gained by improving blood flow to the core. In fact, some data suggest that patients with large infarct cores may be harmed by thrombolytic treatment.

Data from PET scanning studies suggest that the size of the penumbra declines over time, but even at 18 hours, a substantial amount of penumbral tissue may be demonstrated in up to 30% of patients. Identifying patients in whom the penumbra is salvageable regardless of time of onset is paramount in selecting patients for intervention. Below we summarize the 2 most widely available and clinically relevant techniques to evaluate acute ischemic stroke and detect the presence of penumbra.

Magnetic Imaging Studies

Diffusion-weighted imaging is extremely sensitive in the diagnosis of acute ischemic stroke and can be abnormal even within minutes of onset. A reduction in the apparent diffusion coefficient along with a high diffusion-weighted signal correlates to restricted diffusion of water molecules within areas of cellular edema. Perfusion-weighted imaging parameters can be derived after an injection of Gd-based contrast. The difference between the diffusion-weighted MR imaging lesion and the perfusion-weighted imaging lesion is taken to represent tissue at risk for progressing to infarction, which can be saved by restoring blood flow. Data in support of this approach comes from observational studies that have shown smaller final infarct volumes on MR images and improved clinical outcomes in patients treated with thrombolitics irrespective of time (Figs. 1 and 2).

The DIAS (Desmoteplase In Acute Ischemic Stroke) trial was the first randomized study to evaluate the feasibility of using multiparametric MR imaging to extend the time window for treating ischemic stroke. The trial randomized patients with mismatch between diffusion-weighted and perfusion-weighted imaging within 0–9 hours of stroke onset to thrombolytic desmoteplase or placebo treatment. The first part of the study was halted prematurely due to high rates of intracerebral hemorrhage. In the second part, patients were randomized to weight-adjusted doses (60, 90, and 125 μg/kg) of desmoteplase or placebo. Reperfusion rates were significantly higher in the desmoteplase group: 71.4% for the 125-μg/kg group and 19.2% for placebo. In addition, favorable outcome was more common in the desmoteplase group than the placebo group (60% for the 125-μg/kg group vs 22.2% for the placebo). The subsequent DEDAS (Dose Escala- tion of Desmoteplase for Acute Ischemic Stroke) study randomized an additional 37 patients with mismatch between diffusion-weighted and perfusion-weighted imaging within 9 hours and found similar results.

Thomalla and coworkers compared MR imaging–selected patients treated with tPA within 0–6 hours and placebo-treated patients in ECASS, ATLANTIS (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke), and NINDS (National Institute of Neurological Disorders and Stroke) trials. Patients selected for treatment based on MR imaging criteria were more likely to achieve good functional outcome, defined as a mRS score of 1 or less, than patients selected us-
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Fig. 2. Perfusion-weighted CT scans demonstrating an increase in MTT (left) and increase in CBV (right) suggesting the presence of a salvageable penumbra.

ing CT scanning and clinical criteria alone. Furthermore, the rate of symptomatic hemorrhage (3%) was similar to the rate noted in placebo-treated patients (2%) and lower than those in the pooled tPA-treated patients (8%).49

The recent EPITHET (Echoplanar Imaging Thrombolysis Evaluation Trial) randomized patients to rt-PA or placebo 3–6 hours after stroke onset and obtained diffusion- and perfusion-weighted images in all patients.12 Although the study’s primary end point—a decrease in mean geometrical growth of the infarct—was not significantly different between the rt-PA and placebo groups, the investigators did find higher rates of reperfusion with rt-PA compared with placebo in patients with diffusion/perfusion-weighted mismatch. Reperfusion was significantly associated with better neurological outcome.12

In addition to selecting patients who may benefit from thrombolysis, MR imaging may be a powerful tool in identifying those patients in whom thrombolysis may cause harm. The DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Elevation) study evaluated the MR imaging profiles of patients treated with rt-PA 3–6 hours after symptom onset.2 Patients without a diffusion/perfusion-weighted imaging mismatch did not benefit from early reperfusion and individuals with large diffusion- and/or perfusion-weighted MR imaging–documented lesions had more frequent symptomatic intracerebral hemorrhage upon reperfusion. Similarly, the authors of a retrospective study of 650 patients found an almost 6-fold increase in symptomatic intracerebral hemorrhage for patients with large (>100-ml) diffusion-weighted imaging–documented lesions compared with patients with moderate or small infarct volumes.57

To date, few studies have evaluated the utility of perfusion-weighted MR imaging in selecting patients for endovascular treatment.23 Preliminary data suggest that a combined intravenous and intraarterial tPA approach may be beneficial beyond conventional time windows when patients are selected by the presence of perfusion-weighted MR imaging mismatch.23 The ongoing MR imaging–based RESCUE (Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Noninvasive Ex-

aminations) trial, which aims to identify patients who may benefit from mechanical thrombectomy based on baseline MR imaging profiles, may provide additional information.

Computed Tomography Scanning Studies

Noncontrast CT has been the primary modality of choice in the evaluation of acute ischemic stroke since the early 1970s.44,53 It is primarily used in the identification of intracerebral hemorrhage, parenchymal ischemic changes, and stroke mimics. Ischemic changes include sulcal effacement, loss of gray/white matter differentiation or hypodensity, and hypodensity.

Early ischemic changes on noncontrast CT hold some clinical predictive abilities. Studies have shown that the risk of hemorrhagic transformation of ischemic stroke is higher and no clinical benefit is derived from treatment if there is documentation of hypodensity involving more than one-third of the MCA territory.51 The ASPECT (Alberta Stroke Program Early CT) scale is an instrument that is useful in assessing the extent of ischemic findings in the MCA territory on CT scans.44,53 The scale classified a normal brain as represented by a score of 10, and for some ischemic findings involving different parts of the MCA territory, a point is subtracted for each change. An ASPECT score of more than 7 predicts a better outcome after thrombolysis, whereas an ASPECT score of 7 or less reflects a higher risk of hemorrhagic transformation following thrombolysis.44 Both PET and MR imaging studies suggest that areas of hypopattenuation on CT scans represent decreased CBV that could be an indicator of the infarct core, whereas areas of sulcal effacement have been shown to represent areas of increased CBV that may correlate with the penumbra that could be saved with thrombolytic therapy.8,17,44

Computed tomography perfusion scanning is more sensitive than noncontrast CT in identifying ischemic stroke in patients presenting less than 12 hours after ischemic stroke symptom onset and in detecting the extension of the infarction.54 A large rapid bolus of iodine-based contrast material is injected during continuous rapid scanning of one or multiple slices at fixed time interval and the wash-in and wash-out of the bolus can be analyzed by a computer. Maps of regional CBF, CBV, MTT, and time to peak can be generated from the tissue-time density curve. Cerebral blood flow is proportional to the top of the curve and CBV to the area under the curve.44 As in perfusion-weighted MR imaging, the optimal definitions of ischemic core and penumbra have not been established. The difference between CBF and CBV or MTT and CBV is commonly used as a marker for the presence of mismatch with the CBV lesion volume representing the core and the CBF or MTT lesion volume hypoperfused tissue.52

Clinically, CT perfusion offers several advantages over MR perfusion including faster acquisition times and wider availability. Disadvantages include longer postprocessing times, inability to image the whole brain, and potential for anaphylactic or nephrotoxic reactions to iodine-based contrast agents. The main advantages and disadvantages of the 2 perfusion modalities are summarized in Table 1.
Despite its wide availability, CT scanning has been explored in few studies for patient selection for treatment. Recently, Abou-Chebl studied the efficacy and safety of intraarterial therapy including intraarterial tPA, mechanical embolectomy, or angioplasty with or without stenting in patients presenting with acute ischemic stroke less than 6 hours (early) and greater than or equal to 6 hours (late) based on CT perfusion scanning for anterior circulation mismatch or clinical–MR imaging mismatch for posterior circulation, rather than time. The mean time to treatment was 3.4 ± 1.6 hours for the early-onset group and 18.6 ± 16 hours for the late-onset group. Successful recanalization (Thrombolysis in Myocardial Ischemia score of 2 or 3) was achieved in 84.0% of all patients (early vs late onset).14,34 Despite being excluded from treatment by current guidelines, patients including perfusion imaging findings. Diffusion/perfusion-weighted imaging mismatch was present in 79% of patients with wake-up stroke who were imaged within 3 hours of stroke detection similar to 82% of those with known onset time.14 These findings confirm that a significant proportion of patients with wake-up strokes may benefit from treatment, and in fact preliminary evidence suggests that these patients may undergo intravenous thrombolytic or endovascular therapy with similar results to patients treated under current guidelines.23

Patients who have suffered a transient ischemic attack or minor stroke who are at risk of developing worsening symptoms may also be potential candidates for treatment and can be identified through perfusion imaging.1,14 In a recent study of patients with anterior circulation transient ischemic attack who underwent CT perfusion scanning, approximately one-third had perfusion deficits.41 Subsequent in-hospital events were significantly more common in patients with defects documented on perfusion imaging than in those without such defects (22.7% vs 0%, respectively). Furthermore, patients with perfusion defects were more likely to have ipsilateral arterial stenosis, which may represent a target for surgical or endovascular early intervention.41

**Limitations of Perfusion Imaging**

Despite optimism surrounding the use of advanced neuroimaging to select patients for ischemic stroke treatment, this strategy remains far from being widespread. To date, perfusion/diffusion imaging is typically limited to academic or specialized medical centers with expertise in acute stroke management and neuroradiology. Furthermore, some authors have questioned the reliability of MR perfusion imaging in predicting final infarct volumes. Perfusion-weighted PET studies suggest that acute diffusion-weighted lesions may contain areas of penumbra as well as infarct, thus overestimating the size of infarcted tissue,19 while some authors have shown that the mismatch may overestimate the penumbral size.30 Optimal definitions of penumbra/mismatch and standardized perfusion parameters across studies are lacking, and individual parameters may vary in their predictive abilities.16,27,30

The results of the recent DIAS-2 trial have also reinvigorated the debate over perfusion imaging and patient selection.21 Similar to the previous DIAS and DEDAS, the DIAS-2 trial randomized patients 3–9 hours after symptom onset and selected individuals based on the presence of a mismatch for treatment with desmoteplase or placebo. The primary outcome measure of a composite improvement in NIHSS, Barthel Index, and mRS score was similar in the placebo and desmoteplase groups, whereas rates of symptomatic intracerebral hemorrhage were higher in the treatment group.21 These findings may be unsurprising given the low number of patients in the trial with significant penumbra or visible vessel occlusion suggesting thrombus (30%), which is the ultimate target of thrombolytic treatment. Additional trials to clarify the optimal “penumbral size” and in patients with visible occlusions on vascular imaging are needed.

**Conclusions**

Currently, few patients with ischemic stroke receive...
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thrombolytic therapy in part because of the 3-hour-window requirement established by guidelines. Advanced MR perfusion and CT perfusion imaging may play an important role in identifying both patients who may still benefit from or be harmed by thrombolytic therapy outside of conventional time windows.\textsuperscript{3,12,19} Perfusion imaging may also help to identify patients who are at risk of further neurological deterioration and should be considered candidates for early intervention.\textsuperscript{41} Additional studies to validate and standardize perfusion parameters are needed before this approach can be recommended for widespread use.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Authors contributions to the study and manuscript preparation include the following. Conception and design: Duffis, Gandhi. Drafting the article: Duffis, Al-Qudah. Critically revising the article: Prestigiacomo, Gandhi.

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