MRI-guided selection of patients for treatment of acute ischemic stroke

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Purpose of review
To summarize what is known about the use of MRI in acute stroke treatment (predominantly thrombolysis), to examine the assumptions and theories behind the interpretation of magnetic resonance images of acute ischemic stroke and how they are used to select patients for therapies, and to suggest directions for future research.

Recent findings
Recent studies have been contradictory about the usefulness of MRI in selecting patients for treatment. New MRI models for selecting patients have emerged that focus not only on the ischemic penumbra but also on the infarct core. Fixed time-window selection parameters are being replaced by timing-based individualized MRI stroke features. New ways to interpret traditional MRI stroke sequences are emerging.

Summary
Although the efficacy of acute stroke treatment is time dependent, the use of fixed time windows cannot account for individual differences in infarct evolution, which could potentially be detected with MRI. Although MRI shows promise for identifying patients who should be treated, as well as excluding patients who should not be treated, definitive evidence is still lacking. Future research should focus on validating the use of MRI to select patients for intravenous therapies in extended time windows.

Keywords
infarct, MRI, penumbra, stroke, tissue plasminogen activator

INTRODUCTION
MRI has an established role in the diagnosis and evaluation of acute ischemic stroke but has not been validated for identifying patients who would benefit from acute intervention with intravenous (i.v.) thrombolysis or intra-arterial revascularization procedures [1]. Currently, treatment selection is based on fixed time windows, with the only imaging component being exclusion of intracranial hemorrhage (ICH) or extensive completed infarction. Although MRI can be used for this purpose, head computed tomography (HCT) is also able to provide these minimal imaging criteria. MRI, however, provides physiologic data that may allow us to individualize care and increase the number of patients who can be treated safely. MRI is commonly used as a clinical tool based on the concept of the diffusions–perfusion mismatch despite the absence of proof that this is the correct approach.

Occlusion of a cerebral blood vessel can result in an area of physiologically dysfunctional, non-infarcted tissue surrounding an infarcted core [2]. This so-called ischemic penumbra is shown schematically in Fig. 1 and is thought to be due to collateral circulation. A basic assumption is that in the absence of recanalization the infarcted core will grow to consume the ischemic penumbra (Fig. 1a) due to inadequate collateral blood flow. A further assumption is that MRI can approximate the ischemic penumbra as a mismatch between perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI), as shown in Fig. 1b [3]. These assumptions have been at the root of most MRI research on acute stroke treatment in the past decade. More recently, attention has focused on the properties of the infarcted core, rather than just on the ischemic penumbra. It has been hypothesized...
that MRI can identify an unstable core which, if reperfused, can result in complications such as hemorrhage or edema (Fig. 1c) [4].

Tissue plasminogen activator (tPA) is a thrombolytic agent commonly administered to patients with acute stroke and has been effective in improving functional outcomes [5]. The commonly assumed mechanism of tPA is clot lysis within the obstructed vessel, restoring blood flow and preventing infarct growth. This mechanism of action is captured with the penumbra model (Fig. 1a) which drove research focused on MRI measures of mismatch (Fig. 1b) [3]. However, tPA also has effects on the core infarct that are less well understood [6,7]; MRI provides information about the core infarct that may be able to better guide therapy. As tPA is known to be an effective stroke treatment, the unstable core model is aimed at maximizing the number of patients who can safely receive the drug, but does not directly address the question of why a stable core would benefit from the treatment. This review will examine MRI models of the unstable core that used T2 signal change, volume of DWI or PWI lesions, focal cerebral blood volume (CBV) deficits, and blood–brain barrier (BBB) disruption to study the interactions of tPA with core infarction.

There are three types of MRI research for acute stroke treatment: off-label studies in which MRI is used to make treatment decisions without randomization or a control group, observational studies in which MRI is collected but not used, so that possible applications can be assessed, and randomized control trials in which MRI is tested to determine if it can improve outcomes. Ideally, off-label studies would be minimized, observational studies would precede randomized control trials, and randomized control trials would be based on data from observational studies.

This review is organized into sections based on the potential role for MRI in accepted treatment time windows, unknown time windows, and extended time windows. This structure aims to clarify how MRI may influence current practice.

**FIGURE 1.** Panel a shows a schematic of how the infarcted core is hypothesized to expand to incorporate the ischemic penumbra if blood flow is not restored. Panel b shows a schematic of how diffusion and perfusion imaging is used to approximate the ischemic penumbra. Panel c shows a schematic of the unstable core in which restoration of blood flow to the infarcted core results in deleterious consequences.
The ultimate goal for MRI research in the field of acute stroke imaging is to move away from time-based approaches. The use of time to guide treatment stems from the observation that when the entire stroke population is pooled together their benefit from therapy, on average, declines with time. This has been dubbed the ‘epidemiologic clock’ and is a weak approximation of the pathologic state of any given individual, leaving out many other factors that may contribute to better patient selection [8]. The goal of MRI-guided research is to formulate a unifying MRI paradigm that caters treatment to each individual’s ‘brain clock’ [9].

MRI-GUIDED USE OF INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR IN FOOD AND DRUG ADMINISTRATION OR AMERICAN HEART ASSOCIATION TREATMENT TIME WINDOWS

The only Food and Drug Administration (FDA)-approved treatment for acute ischemic stroke is i.v. tPA administered within 3 h from onset [5]. The American Heart Association (AHA) guidelines have extended this therapy to 4.5 h for some populations [10]. Administration of tPA in FDA- or AHA-approved windows is initiated after brain imaging has ruled out ICH. HCT, because of availability and speed of use, has been the imaging modality most widely employed. There has been reluctance to use MRI, which takes longer to acquire than HCT, on the basis of population studies that have found that time to treatment is associated with response to therapy [11]. Thus, to justify its use, MRI must provide novel information that can better direct management than HCT.

Unfortunately, there have been no randomized control trials comparing MRI to HCT in the FDA-approved time window. Observational studies are lacking, and most of our knowledge about i.v. tPA in MRI-selected patients in the 4.5-h window comes from reports of off-label use. Several centers do routinely use MRI-based screening protocols in the acute stroke population [9]. Using MRI has been shown to be feasible in FDA or AHA time windows [12]. A nonrandomized study found that a cohort of patients selected for i.v. tPA using MRI to confirm the presence of a mismatch and absence of a large DWI lesion had better outcomes than a population selected using computed tomography (CT) [13]; however, the modality used was based on availability and feasibility of the MRI, which may have introduced bias.

Although MRI provides a wealth of information about acute ischemic stroke [14], how this information might guide management is unclear. A multicenter trial of HCT vs. MRI in detecting ICH was stopped early because MRI was identifying cases of ICH that were not seen on HCT [15] and it was not known how to use this additional information. Although seemingly intuitive, it has yet to be proven that the increased sensitivity of MRI to ICH will translate into better outcomes [16]. On the basis of the MRI penumbra model (Fig. 1b), some groups may advocate not treating patients whose DWI lesion is equal to their PWI lesion. Others may argue that DWI lesions are reversible in this time window [17] and thus the penumbra model is flawed; however, complete DWI reversal after i.v. tPA is rare [18\*]. The role of DWI reversal is controversial [19–24], but it implies that tPA is positively affecting the core, rather than aggravating it, as is assumed in the unstable core model (Fig. 1c). This could also be part of the explanation for the efficacy of tPA in small vessel (lacunar) strokes [25], which are not captured by the penumbra model (Fig. 1a).

Another argument for using MRI is to exclude stroke mimics, which accounted for one-third of the patients evaluated for stroke in one study [26]. Studies looking at the risks associated with treating stroke mimics have found them to be minimal [27,28]. A serious systemic hemorrhage rate of 1.1% is associated with the population-wide administration of tPA [29], which is presumably independent of cerebral ischemia; it is not known if such a rate would apply to a population of stroke mimics. Presumably, withholding tPA from patients who are MRI-negative would exclude some true strokes from therapy. DWI-negative stroke rates have been reported from 6 to 10% and occur more frequently in the posterior circulation [30–32]. The addition of PWI may reduce the occurrence of MRI-negative strokes but may still miss lacunar strokes [33].

MRI in this window could also identify patients who are rapidly improving but likely to decline because of early recurrence, such as can be seen with a symptomatic vascular stenosis. Patients who are rapidly improving or have low National Institutes of Health Stroke Scale are frequently not treated and yet will go on to sustain substantial disability in almost one-third of cases [34]. DWI or PWI may be able to detect these patients [35,36] as well as transient ischemic attack patients who may benefit from therapy [37]. Thus, in addition to excluding patients who would not benefit from therapy, MRI selection may also lead to inclusion of patients who might have otherwise not been treated.

In summary, MRI’s role in guiding treatment with i.v. tPA in the FDA or AHA time windows remains unclear. Although specific applications...
may seem intuitive, they need to be tested in a controlled fashion. The overall impact of MRI in this time window will be to decrease the number of patients receiving tPA by excluding patients who will not benefit. Future research should focus on observational studies, in which MRI is collected but not used, such that the results can be used to design a randomized trial of MRI vs. CT.

MRI-GUIDED USE OF INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR IN UNKNOWN TIME WINDOWS

Using current fixed time-window stroke treatment paradigms, if a patient has an unknown time-of-onset, treatment cannot be given. This is the ideal population for MRI to help guide treatment. Recent research about using i.v. tPA in patients who have uncertain times-of-onset has largely been motivated by the time dependence of the T2 signal change on fluid attenuated inversion recovery (FLAIR) sequences in areas associated with a DWI-positive stroke [38]. This has been labeled DWI–FLAIR mismatch, a phrase that is somewhat misleading as it is not meant to identify salvageable tissue. FLAIR-negative stroke may be a more appropriate term. The time dependence of T2 signal change has been exploited in an attempt to identify patients who are likely to be within 4.5 h from stroke onset. The attempt, however, to use a more precise measure (the tissue clock) to approximate a less precise measure (the time of onset) may accelerate the time course of T2 signal change on FLAIR images of acute stroke in an unknown time window [44]. Two multicenter clinical trials, Magnetic Resonance (MR) WITNESS and WAKE-UP, are recruiting patients to test the hypothesis that i.v. tPA is safe and effective when administered to patients with an unknown time-of-onset and a FLAIR-negative stroke on MRI.

One unaddressed aspect of the time course of T2 signal change on FLAIR images of acute stroke in these studies is the role of reperfusion. Figure 2 shows an MRI scan of a patient who presented acutely to our institution. The DWI image suggests that there was an initial embolus at the bifurcation of the middle cerebral artery (MCA) resulting in infarction of the entire MCA territory. The PWI suggests that the embolus subsequently propagated into the superior division of the MCA resulting in reperfusion of the inferior division of the MCA. On the FLAIR image, there is a marked difference in the amount of T2 signal change when comparing the tissue supplied by the still-blocked superior division of the MCA (yellow circles) to the now reperfused inferior division of the MCA (red circles). While only a single case, this example suggests that reperfusion may accelerate the time course of T2 signal change. It also complicates our understanding of how T2 signal change fits into the unstable core model (Fig. 1c) as T2 change may reflect both severity of damage and degree of reperfusion. Although several of the studies discussed above reported collecting PWI in their datasets [38,39,43], they do not report what role reperfusion status may play in the rate of T2 signal change.

In conclusion, FLAIR-negative stroke appears to be a reasonable target for patient selection in tPA trials of unknown onset given its specificity for identifying patients within less than 4.5 h from onset (a population known to benefit from i.v. tPA). However, T2 signal change on FLAIR remains poorly understood, and variation with Tesla strength and reperfusion status could confound ongoing multicenter clinical trials. Further studies should focus on understanding the pathophysiology of this phenomenon better.
The use of i.v. tPA in patients beyond FDA or AHA time windows has failed to show benefit in multiple randomized placebo-controlled trials [47,48]. It has been theorized that MRI can select patients who are more likely to benefit from i.v. tPA in an extended time window based on the penumbra model (Fig. 1b). Additionally, MRI may be able to decrease the complication rate by excluding at-risk patients using the unstable core model (Fig. 1c). Non-randomized retrospective studies have supported this approach [49–51]; however, the hypothesis has not been prospectively tested. Most of our understanding about how MRI could be used in this population has come from the combined post-hoc analysis of the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) trial [52] and the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) [53]. These trials had an observational design in which imaging data were collected but not used for treatment decisions. This allowed for an objective assessment of how the MRI data collected could have been relevant. Both trials collected multimodal MRI before and after treatment with i.v. tPA in the 3–6-h window and were predicated on the penumbra model (Fig. 1b). There were some differences in the timing of follow-up scans, additionally EPITHET had a placebo arm. Extensive post-hoc analysis of these two trials, both individually and together, has improved our knowledge of how MRI infarct features relate to each other, evolve over time, and respond to therapy.

The most important concept to emerge from the pooled DEFUSE or EPITHET analysis is that of the malignant profile. The term was initially coined after interim analysis at the midpoint of the DEFUSE trial revealed there was an MRI pattern associated with ICH and poor outcomes after i.v. tPA [52]. Attention was drawn to the volume of the ischemic core and the volume of severe hypoperfusion. Volumetric analysis of the EPITHET population also found an association between large perfusion deficits and poor outcomes [54]. Pooled analysis of the two trials found that not only does the malignant profile increase the risk of ICH and poor outcome, but that if reperfusion was achieved, this risk was much higher [4]. This finding, although not prospectively validated, evokes the tenant of ‘First, do no harm’ in the treatment of acute stroke and has the potential to be relevant in all types of treatments provided in an extended time window [55]. Thus, the malignant profile was the first MRI model of the unstable core (Fig. 1c).

Although MRI has improved our understanding of infarct behavior in response to tPA in an extended
time window, the question remains of how to use this in management. A meta-analysis of trials using the penumbra model (Fig. 1b) concluded that evidence was insufficient to recommend the use of MRI in treatment decisions but strong enough to warrant a phase-3 trial [56]. Although EPITHET failed to demonstrate its primary end point of infarct growth attenuation with tPA, a reanalysis of the data using coregistration (which is more precise than volume comparisons) showed that tPA did significantly decrease infarct growth compared with placebo [57]. Applying the coregistration approach to the pooled DEFUSE and EPITHET dataset demonstrated both attenuation of infarct growth and increased reperfusion [58**]. This validates the penumbra model (Fig. 1b) for tPA use. Despite success with this imaging end point, there was no difference in clinical outcomes or mortality between the tPA and placebo groups. The percentage of patients with a good outcome was 40 and 38% in the tPA and placebo groups, respectively. The symptomatic ICH rate was 7.6 vs. 0%, which may partly explain the lack of clinical benefit. In the International Stroke Trial 3, in which patients were treated with i.v. tPA up to 6 h without MRI-based selection, the symptomatic ICH rate was only 7% [48]. This suggests that the penumbra model, unlike the unstable core model, does not accurately identify patients at risk for hemorrhage, as the bleeding rate between these two trials was similar. The next logical step was to combine the penumbra model, which identifies patients who may benefit, with the malignant profile, which excludes patients who may bleed because of unstable core, into a target profile. This was done for the DEFUSE 2 trial [59]; however, the treatment was changed to intra-arterial therapy, leaving the i.v. question unanswered.

As models have shifted toward identifying the unstable core infarct, additional MRI features have emerged that may improve its accuracy. CBV can be calculated from PWI as the area under the concentration curve. In patients receiving tPA in an extended time window, areas of low blood volume or zero blood volume (absent delivery of contrast) were associated with subsequent ICH [60]. The theory that very low CBV (VLCBV) is associated with hemorrhagic transformation was tested in the EPITHET dataset [61]. This initial study identified a CBV threshold for which even a small volume of VLCBV was sensitive for detecting subsequent parenchymal hematoma, the most severe form of ICH (as opposed to hemorrhagic infarction). This threshold was then tested in the DEFUSE dataset and again was very sensitive for detecting patients at risk for parenchymal hematoma and outperformed DWI and PWI volume measures [62**]. This threshold has been validated by a different group in a unique dataset [63**].

Although VLCBV, as it has been defined, shows promise as a clinical tool, further work is needed to understand the mechanism by which it is identifying an unstable core. It is known that when PWI is used to calculate CBV of a brain tumor, the volume can be underestimated if gadolinium leaks through BBB [64]. BBB damage in stroke patients detected by gadolinium leakage on MRI has been associated with ICH [65,66]. Thus, it is possible that BBB damage is the relevant variable with VLCBV. The effect of BBB damage on CBV can be corrected for [64], but should include an arrival-time correction [67] when applied in the setting of PWI deficits. BBB damage would only be detected in this manner if gadolinium reaches the tissue, unlike VLCBV in which little or no contrast reaches the tissue. If VLCBV is the cause for ICH, then permeability imaging of BBB damage would be negative in these cohorts. Figure 3 shows a patient who presented to our institution with an acute ischemic stroke outside the window for tPA. BBB damage was detected using in-house software [67], and follow-up imaging demonstrated hemorrhagic conversion of the stroke in the area of the initial BBB damage.

In conclusion, there is preliminary evidence that MRI can help select patients for treatment with i.v. tPA in an extended time window; however, this has not been tested prospectively. The optimal MRI profile to detect an unstable core has not been established and needs further investigation.

MRI-GUIDED USE OF INTRA-ARTERIAL THERAPIES

The use of MRI to guide patient selection of intra-arterial therapies for acute stroke treatment is a controversial topic, as is the use of intra-arterial therapies in general. The difficulty with research focused on this topic is that it tests an experimental method (MRI-guided selection) with an experimental treatment (intra-arterial therapy), which makes the results difficult to interpret. Nonetheless, two large multicenter National Institutes of Health funded trials, DEFUSE 2 [59] and MR Rescue [68], were recently completed, reporting very different results. The possible reasons for how such different conclusions were reached by these two trials have been examined [69**] and are beyond the scope of this review. Suffice to say that the basic principles of the penumbra and core remain key.

Adding MRI to an existing CT-based selection process at a large volume stroke center [70**] cut the rate of patients taken to intra-arterial therapy in half and doubled the rate of favorable outcomes even when taking into consideration the patients
excluded from therapy. While far from a randomized trial, this study, along with others looking at feasibility [71], offers a compelling argument not to give up on using MRI to select or exclude patients. But ultimately, effectiveness of intra-arterial therapy will need to be established before the role of MRI in this process can be appropriately addressed. There is no evidence that intra-arterial, even when used in combination with i.v., is better than intravenous tPA alone [72,73].

**CONCLUSION**

There continues to be substantial research devoted to understanding the role of MRI in acute stroke treatment. The most useful studies have been observational, in which an MRI is collected but not used for decision making. Randomized control trials are scarce or ongoing. There are potential applications of MRI in early time windows, but they have not been rigorously tested. Observational studies are needed in this time window to guide future clinical trials. In extended time windows, there is good evidence that using i.v. tPA, with an MRI profile that combines a penumbral inclusion model with an unstable core exclusion model, will result in improved outcomes. The best profile remains to be determined. Studies of MRI selection for intra-arterial therapies are complicated by the unclear efficacy of intra-arterial therapy itself. While validation of intra-arterial therapy may benefit from MRI selection, this treatment is plagued by inherent time delays, such as time-to-groin-puncture, the elimination of which may provide a better target for designing a successful trial [72,73].

It is sometimes argued, despite the lack of evidence, that intra-arterial therapy is more effective than i.v. therapy in the extended time window. Pooled analysis of DEFUSE 1 and DEFUSE 2 allowed for comparison of reperfusion rates for patients receiving i.v. vs. intra-arterial therapy in an extended time window [74**]. The degree of reperfusion was the same regardless of whether i.v. or intra-arterial therapy was employed. The 90-day functional outcomes also did not differ between the two studies. Thus, there is no evidence for intra-arterial therapy over i.v. therapy in an extended time window. Future trials should focus first on how MRI can better select patients for i.v. therapies.

**Acknowledgements**

Sources of Funding: Richard Leigh is supported in part by NIH R01DC05375 and RO1NS47691 for imaging studies of recovery of function in stroke.

**Conflicts of interest**

There are no disclosures or conflicts of interest.
Neuroimaging

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest


37. This is a fairly large cohort of patients (n = 231) who had MRI scans done before and after administration of i.v. IPA in approved time windows. Patients were only included if their pretreatment MRI scan was DWI positive. They found that complete sustained reversal of DWI lesions with IPA, while rare, did occur.


This is a post-hoc analysis of pooled observational data that tests if the MRI approximation of the penumbral model (Fig. 1b) is affected by tPA in an extended time window. tPA did significantly decrease infarct growth (Fig. 1a) over placebo; however, clinical outcomes were not different which may have been due to the much higher rate of symptomatic ICH in the iPA group.


This post-hoc analysis of pooled observational data examined an MRI model of the unstable core (Fig. 1c) which they call "VLCBV." They found that even very small regions of VLCBV were associated with the development of severe ICH independent of iPA.


This was a validation study which reproduced the findings of Campbell et al. regarding the role of VLCBV in a unique dataset.


Parsons MW, Albers GW. MR RESCUE: is the glass half-full or half-empty? Stroke 2013; 44:2055–2057.

This is a review of the differences between the DEFUSE 2 and MR Rescue trials that may explain their divergent conclusions. Enrollment biases may have resulted in different populations being recruited for each of the trials.


This retrospective review looked at the effect of adding MRI to an existing CT-based selection process for intra-arterial therapy at a large volume stroke center and found that the rate of patients taken to intra-arterial therapy was cut in half and the rate of favorable outcomes doubled even when taking into consideration the patients excluded from therapy.


This is a post-hoc analysis of pooled observational data from trials in which patients received iV. and/or intra-arterial therapies in extended time windows. They tested a ‘target mismatch (TMM),’ which is a combination of a penumbra model (Fig. 1b) and an unstable core model (Fig. 1c), and found that patients with a TMM responded better to reperfusion than those without a TMM.