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MRI-Guided Selection of Patients for Acute Ischemic Stroke Treatment

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Abstract

Purpose of review—To summarize what is known about the use of MRI in acute stroke treatments (predominantly thrombolysis), to examine the assumptions and theories behind the interpretation of MR images of acute 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 the core infarct. Fixed time-window selection parameters are being replaced by individualized MRI features. New ways to interpret traditional MRI sequences are emerging.

Summary—Although the efficacy of acute stroke treatment is time dependent, the use of fixed time-windows does not account for individual differences in infarct evolution, which could be detected with MRI. While MRI shows promise for identifying patients who should be treated, as well as exclude 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 IV therapies in extended time windows.

Keywords

MRI; Stroke; tPA; Penumbra; Infarct

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 (IV) thrombolysis or intra-arterial (IA) revascularization procedures (1). Currently, treatment selection is based on fixed time-windows, with the only imaging component being exclusion of intracranial hemorrhage or extensive completed infarction.

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Although MRI can be used for this purpose, head CT 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 a commonly used 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 but non-infarcted tissue surrounding an infarcted core (2). This so-called *ischemic penumbra* is shown schematically in figure 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 (figure 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 figure 1B (3). These assumptions have been at the root of most MRI research of 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, results in complications such as hemorrhage or edema (figure 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 (figure 1a) and was the driving force behind research focused on MRI measures of mismatch (figure 1b) (3). However tPA also has effects on the core infarct which are less well understood (6, 7); MRI provides a window into the core infarct which may be able to better guide therapy. Since 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 treatment. This review will examine MRI models of the unstable core (figure 1c) which have utilized T2 signal change, volume of DWI/PWI lesions, focal cerebral blood volume deficits and blood-brain barrier disruption to study the interactions of tPA with core infarction.

There are three area 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 where MRI is tested to determine if it can improve outcome. 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. 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 which 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 IV tPA in FDA/AHA treatment time windows

The only FDA-approved treatment for acute ischemic stroke is IV tPA administered within three hours from onset (5). The American Heart Association (AHA) guidelines have extended this therapy to the 4.5 hours for some populations (10). Administration of tPA in FDA/AHA approved windows is initiated after brain imaging has ruled out intracranial hemorrhage (ICH). Head CT (HCT), due to 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, in order 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 IV tPA in MRI-selected patients in the 4.5-hour 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/AHA time windows (12). A non-randomized study found that a cohort of patients selected for IV 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 CT (13), however the modality used was based on availability and feasibility of the MRI which may have introduced bias.

While 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 not seen on HCT (15) and it was not known how to utilize this additional information. While seemingly intuitive, it has yet to be proven that the increased sensitivity of MRI to ICH will translate into better outcomes (16). Based on the MRI penumbra model (figure 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 IV tPA is rare (18). The role of DWI reversal is controversial (19–24), but such a situation implies that tPA is positively affecting the core, rather than aggravating it, as is assumed in the unstable core model (figure 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 (figure 1A).

Another argument for using MRI is to exclude stroke mimics, which account 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 6-10% 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 due to early recurrence, such as can be seen with a symptomatic vascular stenosis. Patients who are rapidly improving or have low NIHSS are frequently not treated and yet will go on to sustain substantial disability in almost one-third of cases (34). DWI/PWI may be able to detect these patients (35, 36) as well as TIA 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 that might have otherwise not been treated.

In summary, MRI's role in guiding treatment with IV tPA in the FDA/AHA time windows remains unclear. While 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 IV tPA in unknown time windows

Using current fixed time-window stroke treatment paradigms, if a patient has an unknown time of onset, treatment would not be possible. This is the ideal population for MRI to guide treatment. Recent research about using IV tPA in patients who have uncertain times-of-onset has largely been motivated by the time dependence of the T2 signal change on FLAIR sequences in areas associated with a DWI-positive stroke (38). This has been labeled DWI-FLAIR mismatch, a phrase that is somewhat misleading since 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 hours from stroke onset. However the attempt to use a more precise measure (the tissue clock) to approximate a less precise measure (the epidemiologic clock) may undermine our understanding of this phenomenon. In reality, FLAIR-negative stroke is using the unstable core model (figure 1C) such that lack of T2 signal change is identifying a stable core (39).

Single-center studies using 1.5-Tesla scanners report good sensitivity and specificity for FLAIR-negative strokes to be within the 4.5-hour time window (40, 41), with better performance for larger cortical strokes. However single-center studies using 3-Tesla scanners found poorer performance with a loss of sensitivity but preserved positive predictive value (42, 43). This finding is likely due to better detection of early FLAIR change with 3-Tesla scanners and suggests that the approach of dichotomizing strokes as

FLAIR-negative or FLAIR-positive is a crude use of a sophisticated tool. Thus, a multicenter analysis using a mixture of 1.5 and 3-Tesla scanners yielded results falling between those of the two scanner strengths individually (44). An approach to quantify changes using the contralateral hemisphere to normalize the signal change was proposed (45), but other studies have not found improvement with quantification over visual inspection (41, 46).

Since it is unlikely for a FLAIR-negative stroke to be older than 4.5 hours, excluding FLAIR-positive strokes from treatment is a good way to exclude patients beyond 4.5 hours from onset; however patients who are in the 4.5-hour window can be FLAIR-positive (42) and would be eliminated using this method, when they would have been candidates for treatment if they had a known time-of-onset. Although the FLAIR-negative stroke imaging profile will miss some patients who are in fact in the 4.5-hour window, it is felt to have an adequate level of specificity to guide clinical trials of IV tPA in an unknown time window (44). Two multicenter clinical trials, MR WITNESS and WAKE-UP, are recruiting patients to test the hypothesis that IV 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 there was an initial embolus at the bifurcation of the middle cerebral artery (MCA) resulting in infarction of the entire MCA territory. However 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 anecdotal, 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 (figure 1C) since T2 change may reflect both severity of damage as well as degree of reperfusion. Although several of the studies discussed above reported collecting PWI in their datasets (38, 39, 43), neither 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 patients within <4.5 hours from onset (a population known to benefit from IV 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.

MRI-guided use of IV tPA in extended time windows

The use of IV tPA in patients beyond FDA/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 IV tPA in an extended time window based on the penumbra model (figure 1B). Additionally, MRI may be able to decrease the complication rate by excluding at-risk patients using the unstable core model (figure 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 DEFUSE (52) and EPITHET (53) trials. These trials had an observational design such that 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 multi-modal MRI before and after treatment with IV tPA in the 3-6 hour window and were predicated on the penumbra model (figure 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 as pooled analyses, 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/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 outcome after IV tPA (52). Focus 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 outcome (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, while 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 treatment provided in an extended time window (55). Thus the malignant profile was the first MRI model of the unstable core (figure 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 (figure 1B) concluded that evidence was insufficient to recommend the use of MRI-based treatment 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 co-registration (which is more precise than volume comparisons) showed that tPA did significantly decrease infarct growth compared with placebo (57). Applying the co-registration approach to the pooled DEFUSE/EPITHET dataset demonstrated both attenuation of infarct growth and increased reperfusion (58). This validates the penumbra model (figure 1B) for tPA use. However, 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 IST3, in which patients were treated with IV tPA up to six hours without MRI-based selection, the symptomatic ICH rate was only 7% (48). This suggests the penumbra model, unlike the unstable core model, does not accurately identify patients at risk for hemorrhage since the bleeding rate between these two trials was similar. Thus, 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 due to unstable core, into a target profile. This was done for the DEFUSE 2 trial (59); however the treatment was changed to IA therapy, leaving the IV question unanswered.

As models have shifted toward identifying unstable core infarct, additional MRI features have emerged that may improve its accuracy. Cerebral blood volume (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 the blood brain barrier (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 it is 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 where 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 IV tPA in an extended time window, however this has not been tested prospectively. The exact MRI profile to detect an unstable core has not been established and needs further investigation.

MRI-guided use of Intra-arterial (IA) therapies

The use of MRI to guide patient selection of IA therapies for acute stroke treatment is a controversial topic, as is the use of IA 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 (IA therapy) which makes results difficult to interpret. Nonetheless, two large multicenter NIH-funded trials, DEFUSE 2 (59) and MR Rescue (68), were recently completed, reporting very different results. The possible reasons for such different conclusions reached by these two trials has been examined (69) and is 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 IA therapy in half and doubled rate of favorable outcome 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), offer a compelling argument to not give up on using MRI to select or exclude patients. But ultimately, effectiveness of IA therapy will need to be established before the role of MRI in this process can be appropriately addressed. There is no evidence that IA, even when used in combination with IV, is better than IV 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, where 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 IV tPA, when guided with an MRI profile that combines a penumbral inclusion model with an unstable core exclusion model, will result in improved outcomes. However the best profile remains to be determined. Studies of MRI selection for IA therapies is complicated by the unclear efficacy of IA therapy itself. While validation of IA 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 serve a better target for designing a successful trial (72, 73).

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

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time windows. Patients were only included if their pre-treatment MRI scan was DWI positive. They found that complete sustained reversal of DWI lesions with tPA, while rare, did occur.

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Summary Points

A new model for MR imaging of acute ischemia is emerging which is focused on the stability of the core infarct in addition to the ischemic penumbra.

MRI offers the potential to move away from the fixed time-window paradigm for acute stroke treatment and towards an individualized model.

Although the use of MRI to select patients for treatment has not been validated, the strongest evidence points toward MRI-guided selection of patients for IV thrombolysis.

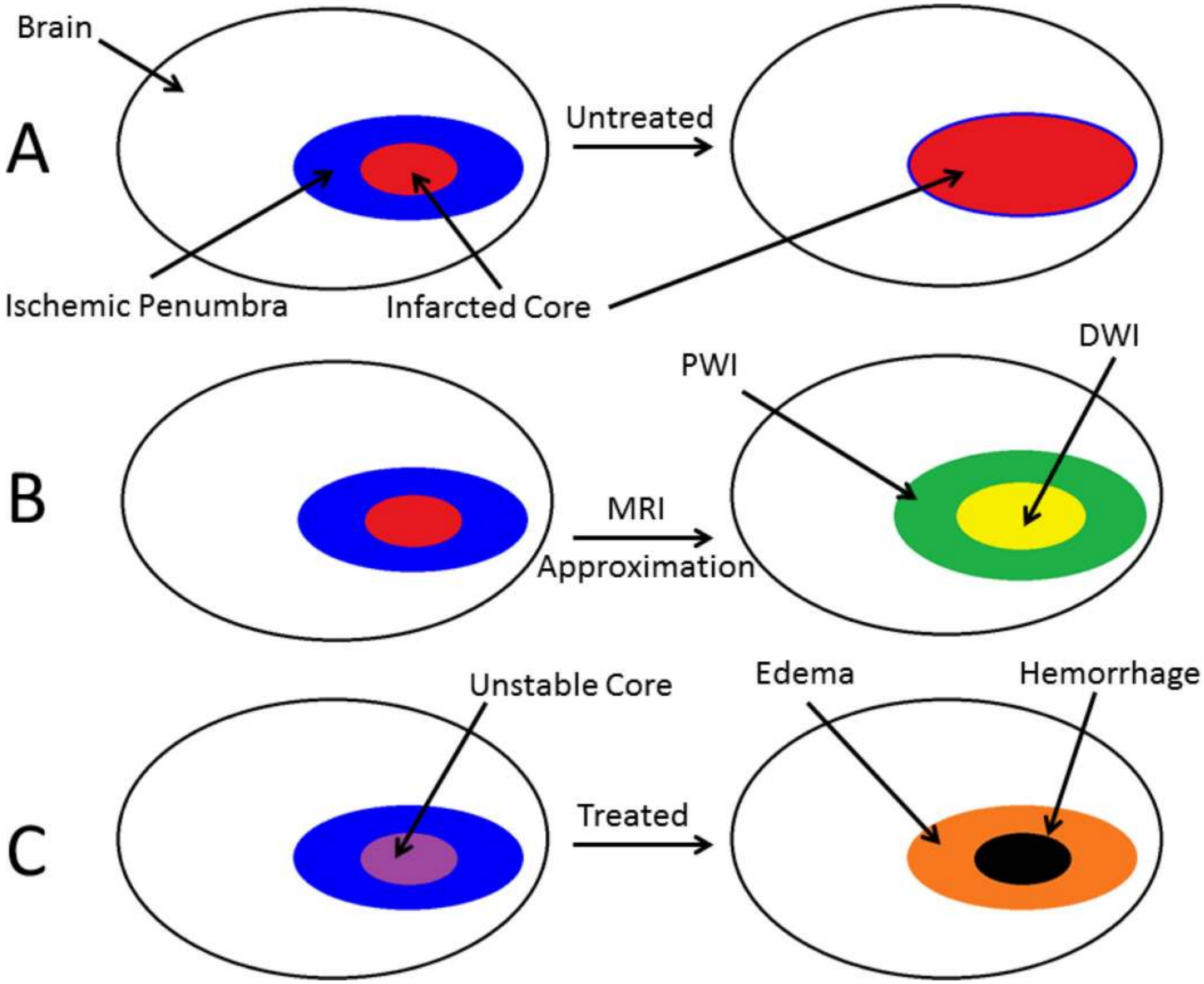

Figure 1.

Panel A shows a schematic of how the infarcted core is hypothesized to grow into 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.

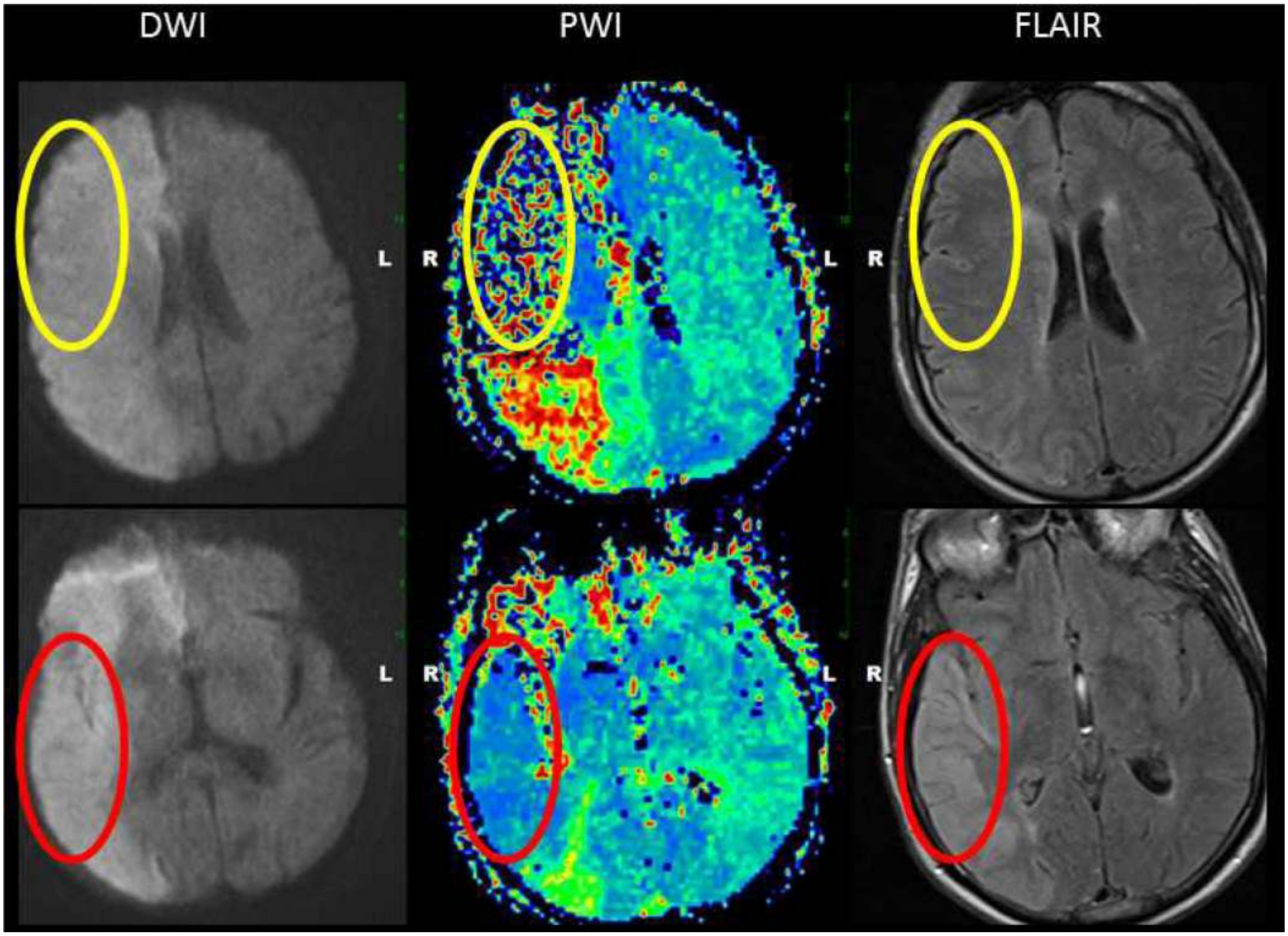

Figure 2.

DWI, PWI and FLAIR sequences from a single time point of an acute ischemic stroke patient are shown. Although the entire MCA territory is infarcted on DWI, the inferior division of the MCA territory (red circles) has experienced reperfusion on PWI, while the superior division territory (yellow circles) has not. On the FLAIR image the T2 signal change is much more advanced in the reperfused territory.

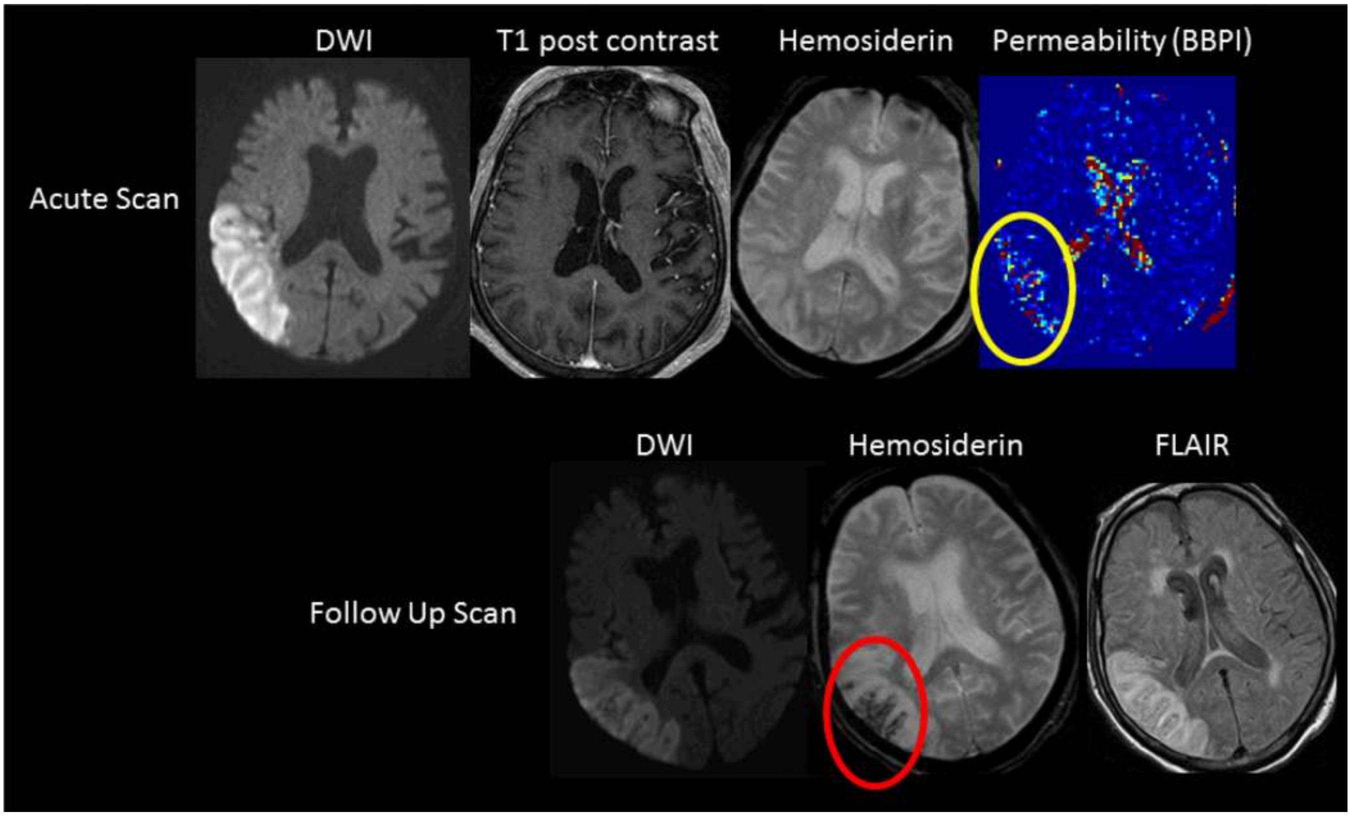

Figure 3.

MRI scans are shown from two time points of an ischemic stroke patient. On the acute scan the DWI positive stroke does not show any blood-brain barrier damage on T1 post contrast imaging or any hemorrhagic transformation on hemosiderin imaging. However blood-brain permeability imaging (BBPI) detects an area of contrast leakage (yellow circle). Follow-up imaging demonstrates hemorrhagic transformation in the area of BBB damage (red circle) seen on BBPI.