Diffusion–perfusion MRI for triaging transient ischemic attack and acute cerebrovascular syndromes
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Purpose of review
Time from symptom onset to treatment is considered to be the key variable that influences the indication of recanalization therapy for treatment of acute brain infarction. Symptom duration less than 24 h defines transient ischemic attack (TIA). The evolution of multimodal brain MRI demonstrates that neuroimaging findings of tissue injury may be more important predictors of clinical outcomes than arbitrary time thresholds.

Recent findings
Preliminary studies suggest that stroke victims with a significant penumbra estimated by the diffusion/perfusion mismatch on MRI benefit from thrombolysis beyond the currently recommended time window of 4.5 h. New software programs can automatically produce reliable perfusion and diffusion maps for use in clinical practice. Combined diffusion and perfusion MRI reveals an acute ischemic lesion in about 60% of TIA patients. Patients with transient symptoms and a restricted diffusion lesion on MRI are considered by the American Heart Association (AHA) scientific committee to have suffered a brain infarction and have a very high risk of early stroke recurrence.

Summary
Multimodal MRI provides critical real-time information about ongoing tissue injury as well as the risk of additional ischemic damage. It is becoming an essential tool for the diagnosis, management and triage of acute TIA and brain infarction.

Keywords
brain infarction, MRI diffusion and perfusion, transient ischemic attack, triage

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Multimodal MRI allows the physician to estimate critical parameters essential to manage acute stroke patients: the diffusion weighted imaging (DWI) sequence confirms the diagnosis of brain infarction and evaluates the extent of the core. Gradient echo imaging and FLAIR are as accurate as head CT to reveal an ICH [13]. Magnetic resonance angiography (MRA) reveals vessel occlusion or stenosis. Perfusion weighted imaging (PWI) gives an estimate of cerebral hemodynamics. The mismatch between the core of the infarction revealed on DWI and the region of critical hypoperfusion estimated by PWI (Figs 1 and 2) has been proposed as a surrogate of the ischemic penumbra [14]. Multimodal MRI also provides essential information for the management of acute TIA: DWI and PWI help to confirm the vascular nature of the symptoms; MRA visualizes a brain or neck vessel symptomatic lesion. Based on these premises several clinical trials have investigated the role of multimodal MRI for the selection of patients for acute stroke treatment and its yield for the diagnosis and prognosis of TIA patients.

**Diffusion**

Severe ischemia induces a failure of adenosine triphosphate (ATP) metabolism that leads to the passive influx of water in the intracellular space resulting in cell swelling called cytotoxic edema. The cytotoxic edema decreases the apparent diffusion coefficient (ADC) [15,16]. Acute brain infarction is revealed on DWI within minutes following its onset. The sensitivity of DWI for the diagnosis of stroke (97%) is significantly higher than the sensitivity of acute head CT (47%) [17].

Malignant infarctions are defined as very large infarctions that progress spontaneously to brain herniation and death. A study has suggested that malignant infarctions were associated with DWI lesions larger than 145 cm$^3$ [18]. Patients with these large acute lesions benefit from emergent craniectomy which has been shown to reduce mortality in this subgroup of patients [19]. Large DWI lesions and low ADC values have been also associated with an increased risk of hemorrhagic transformation after thrombolysis [20]. In the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke (DEFUSE) study, patients with a DWI lesion larger than 100 cm$^3$ treated by tPA 3–6 h after symptom onset had an increased risk of symptomatic hemorrhagic transformation and poor outcomes [21]. Post-hoc analyses

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**Key points**

- Emergent MRI with DWI with neck vessel imaging is now the recommended imaging approach for the evaluation of TIA patients. Perfusion imaging increases the yield of diffusion imaging for the diagnosis of the vascular nature of transient neurological symptoms.
- Diffusion imaging is a valuable tool for the management of severe/malignant infarction. Large and severe lesion on PWI lesion may help to predict hemorrhagic transformation and poor outcome following reperfusion.
- The quantitative estimation of DWI/PWI mismatch is now available for clinical use. Studies are ongoing to evaluate its yield for the selection of patients susceptible to benefit from an acute recanalization.

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**Figure 1** Fifty-year-old male experiencing an acute left middle cerebral artery infarction (National Institutes of Health Stroke Scale score = 22)

Initial MRI performed 3 h after symptoms onset demonstrates a significant mismatch; the diffusion weighted imaging (DWI) lesion of 40 cm$^3$ (a) is surrounded by a large and severe perfusion weighted imaging (PWI) lesion (outlined by $T_{\text{max}}>6$ s) of 125 cm$^3$ (b). The severe perfusion delay (outlined by $T_{\text{max}}>8$ s) was also very large (85 cm$^3$). Despite successful reperfusion demonstrated by PWI imaging performed 6 h later (d), the patient developed symptomatic hemorrhagic transformation on follow-up DWI and FLAIR performed 5 days after symptom onset (c and e). National Institutes of Health Stroke Scale (NIHSS) score was 22 at 1 month.
performed on the DEFUSE–Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) [22] combined dataset suggested that reperfusion was associated with poor outcomes among patients with a DWI lesion larger than 80 cm$^3$ [23]. In another study, a DWI lesion larger than 70 cm$^3$ prior to an intra-arterial stroke therapy predicted a poor prognosis whether or not the recanalization was achieved [24]. These findings suggest that DWI can play a major role in the management of severe stroke to help decide between potentially life-saving surgical decompression vs. potentially deleterious recanalization therapy.

Up to 40% of patients with a TIA exhibit positive DWI MRI after the resolution of the symptoms (Fig. 3) [25]. The American Heart Association (AHA) has recently redefined TIA using a tissue-based definition rather than the traditional 24 h definition. Using the tissue-based definition, TIA is limited to situations where there is no evidence of acute infarction [26]. Cohort studies have confirmed that a positive DWI is an independent risk factor for stroke within the next day after symptom onset [10,12]. Recently, a multicenter study has combined the results of brain imaging with the ABCD2 score and found that this combination significantly improves the prediction of the future risk of stroke [27]. The AHA now recommends that patients with TIA ‘should preferably undergo neuroimaging evaluation within 24 h of symptom onset. MRI, including DWI, is the preferred brain diagnostic imaging modality’ [26].

**Perfusion**

Bolus tracking perfusion imaging is the most commonly used technique to measure cerebral perfusion. The intensity and the delay of the signal change induced by the passage of gadolinium within the capillary generates a time/concentration curve. Critical hypoperfusion is defined, according to the mismatch hypothesis, as the PWI lesion that will predict the extent of final infarction if no reperfusion occurs. Several modalities have been proposed to assess cerebral perfusion such as cerebral blood flow, mean transit time, time to peak or $T_{\text{max}}$ [28,29]. $T_{\text{max}}$ is the time when the residue function reaches its maximum and is obtained by the deconvolution of the arterial input function (AIF) [30]. $T_{\text{max}}$ delays more than 2 s were used in DEFUSE and EPITHET to define PWI lesions [21,22]. A review of the DEFUSE results demonstrated that, among patients who did not reperfuse, a $T_{\text{max}}$ threshold between 4 and 6 s gives a
better estimation of critical hypoperfusion [31*]. This finding is in keeping with the results of direct voxel-based comparisons between MRI-PWI and PET or xenon CT [32,33*]. Lesions outlined by a $T_{\text{max}}$ threshold above 8 s that are larger than 80 cm$^3$ have been a better predictor of poor outcome and symptomatic hemorrhagic transformation following reperfusion than large DWI lesion size (Fig. 1) [23,34*]. Finally, a severe cerebral blood volume (CBV) drop was also associated with the risk of hemorrhagic transformation following tPA administration 3–6 h after symptom onset [35*].

Critical perfusion thresholds are rarely demonstrated in patients with recent TIAs. Hence a qualitative evaluation of nonthresholded PWI maps is preferred to detect the PWI lesions following TIA (Fig. 3). Several studies have demonstrated that PWI lesions are present in about 30–40% of TIA patients, and in many of these cases there are no DWI lesions [36*,37,38]. Therefore, PWI is complementary to DWI and can help confirm the vascular nature of transient neurological symptoms.

Perfusion imaging suffers from technical limitations. First, PWI is unable to provide a reliable quantitative estimation of cerebral perfusion when compared to gold standards such as Xe-CT or PET scan [30*,32,33*,39]. Second, the processing of PWI maps by different software programs results in variable PWI volumes. Therefore, it is essential to standardize the approach to PWI processing.

**New concepts**

The classical organization of an acute ischemic lesion on MRI has been assumed to be a central DWI lesion surrounded by a PWI lesion. However, this pattern is uncommon among patients scanned 3–6 h after symptom onset. At this time-point, part of the DWI lesion has already reperfused [40*,41*]. This ‘early reperfused’ DWI region has a high reversal rate following recanalization and reversal is associated with clinical recovery. This region has been termed RADAR (reversible acute DWI already reperfused) [42*]. Recently the EPITHET group has confirmed a higher reversal rate of the reperfused DWI. They also demonstrated that part of the reversal was in fact related to infarct atrophy (measured at 90 vs. 30 days in DEFUSE), suggesting that DWI reversal was less common than initially estimated [43*]. PWI/DWI mismatch is usually estimated by the ratio or the difference between the PWI and DWI volume. Since part of the DWI lesion may not have a superimposed PWI lesion, this ‘volumetric approach’ to mismatch quantification may underestimate the full volume of mismatch that can be obtained by coregistration of the PWI and DWI images [40*]. Finally, one group has evaluated the yield of acute ADC map to predict final infarction in the case of no recanalization. The mismatch between the measured acute infarction and predicted final lesion is proposed as a surrogate of penumbra, which remains to be evaluated in a prospective study [44*].

**MRI to select patients for acute stroke treatment**

Three studies have investigated the yield of using MRI profiles to select patients for acute stroke treatment. DEFUSE and EPITHET tested the mismatch hypothesis based on quantitative estimation. In these two studies, both DWI and PWI volumes were calculated after patient enrollment and patient outcomes were compared based on MRI profiles. The Desmoteplase In Acute Stroke (DIAS) 2 study selected patients for enrollment based on the presence of mismatch performed by a qualitative ‘eyeballing’ approach [45*].

DEFUSE [21] was a phase 2 study that used open label tPA in 74 patients with an acute ischemic stroke within 3–6 h after symptom onset. The primary hypothesis was that prespecified MRI profiles could identify patients who will have a favorable outcome if early reperfusion occurs following tPA treatment. Forty patients had a mismatch defined as a PWI lesion ($T_{\text{max}} > 2 s$) 1.2 times larger than the acute DWI lesion. Both reperfusion ($P = 0.04$) and recanalization ($P = 0.01$) were associated with favorable outcomes in mismatch patients, but not in patients with other MRI profiles. This relationship was even more apparent among the subgroup of mismatch patients who did not have a malignant profile (DWI and/or PWI $T_{\text{max}} > 8 s$ larger than 100 cm$^3$).

EPITHET [22] was a phase 2 randomized double-blind placebo-controlled clinical trial in which 101 patients with an acute hemispheric stroke were randomized to receive tPA ($n = 52$) or placebo ($n = 49$) within 3–6 h after symptom onset. The primary efficacy endpoint was the reduction of infarct growth among mismatch patients. Follow-up MRI was performed 3–5 days and 90 days after symptom onset. The authors used the same mismatch definition as in DEFUSE, however PWI processing methods differed. The study failed to demonstrate a statistically significant attenuation of infarct growth in the tPA group; however, some of the secondary outcome measures were positive. In addition, similar to the DEFUSE results, reperfusion was strongly associated with good clinical outcome and reduced infarct growth among mismatch patients.

Desmoteplase is a newer thrombolytic agent with better fibrin specificity than tPA [45*]. The primary hypothesis of the DIAS-2 study was that desmoteplase, administered within 3–9 h after symptom onset, will improve clinical recovery in mismatch patients. Eligible patients had at least a 20% PWI/DWI mismatch or CT perfusion-based
mismatch, qualitatively estimated at each participating center. DIAS-2 was a multicenter, placebo-controlled, double-blind, dose ranging study. Patients were randomly assigned to 90 µg/kg desmoteplase (n=57); 120 µg/kg desmoteplase (n=66) or placebo (n=63). Most of the patients were enrolled based on MRI data (60%); CT perfusion was used in 40%. The median baseline National Institutes of Health Stroke Scale (NIHSS) score was 9 which is low compared to DEFUSE (11.5) and EPITHET (13). The mortality rate was increased in the 125 µg/kg group (21%) compared to 6% in the placebo group. Clinical recovery occurred in only 36% of the 125 µg/kg group compared to 46% in the placebo group and 47% in the 90 µg/kg group. A post hoc analysis found that 15% of the enrolled patients had no mismatch which was consistent with a recent substudy of EPITHET that suggests a qualitative ‘eyeball approach’ to mismatch identification is not highly accurate [46]. Furthermore, only 30% of the enrolled patients had a visible vessel occlusion at baseline.

Future directions

Three studies are currently investigating the value of an automated, quantitative real-time approach for identifying favorable candidates for reperfusion therapies. Two studies involve patient selection for intra-arterial procedures: MR Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) is using a multiparametric algorithm to define penumbral tissue. DEFUSE 2 is using a quantitative evaluation of the ADC to determine core and T_max more than 6h threshold to outline critical hypoperfusion. The Extending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) uses the same DWI/PWI analysis program as DEFUSE 2 (RAPID) to identify mismatch patients to enter into a randomized trial comparing tPA vs. placebo 4.5–9h after symptom onset [47].

Conclusion

MRI with DWI, in conjunction with neck vessel imaging, is now the recommended imaging approach for the urgent evaluation of TIA patients. The addition of PWI may improve the yield of MRI for TIA diagnosis, and studies are needed to investigate its impact on the estimation of stroke risk.

Diffusion MRI is a valuable tool to assist in the management of severe/malignant brain infarctions. In addition, recent studies suggest that large and severe PWI lesions may predict poor outcome following reperfusion.

Previous studies have demonstrated that a quantitative estimation of DWI/PWI mismatch can identify patients who are likely to benefit from early reperfusion. The use of ADC and PWI threshold techniques appears to improve the identification of the core and the extent of the salvageable brain tissue. New software programs that implement these advances are now able to generate quantitative PWI and DWI maps within minutes. Some experts now recommend the use of PWI/DWI mismatch to select patients for acute recanalization therapy [48], others await validation in the ongoing and future trials [47].

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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

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 91).

4 Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010; 375:1695–1703. This meta-analysis confirmed that patients selected by clinical symptoms and CT benefit from intravenous alteplase when treated up to 4.5h but not after.
14 Donnan GA, Baron JC, Ma H, Davis SM. Penumbral selection of patients for trials of acute stroke therapy. Lancet Neurol 2009; 8:261–269. Interesting review that describes the performance and limitation of multimodal MRI to outline the penumbra. It also introduces the notion of the geography and structure of the ischemic lesion and its impact on mismatch definition (other references on the subject [40*,41]).
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25 This study compared back-to-back PWI MRI and Xe-CT among patients with a subacute brain infarction. Its results confirm that Tmax more than 6 s gave the best measurement of critical hypoperfusion and also showed the limitation of PWI MRI for the quantitative assessment of cerebral hemodynamics.


32 This study shows that the classical centripetal distribution of an acute DWI lesion surrounded by PWI is rarely found.


37 This study shows that the highest reversal rate of the DWI lesion is already reperfused (before treatment). This region had a higher reversal rate than the rest of the DWI lesion.


39 This EPITHET substudy confirms that part of the DWI lesion already reperfused had the highest reversal rate, but shows that a significant part of the observed diffusion reversal (40%) is related to the intact associated brain atrophy.


41 This group proposes a semi-automated processing of acute ADC map to predict final infarction. They obtained a good correlation between predicted and measured final infarct among noncanalizers, and proposed the use of the mismatch between acute infarction and predicted final lesion as a surrogate of the penumbra.


43 DIAS was the first study that applied the penumbra selection for thrombolytic treatment of acute ischemic stroke. Its negative results underline the limitations of the qualitative (eyeballing) estimation of the mismatch.
