Diffusion–perfusion MRI for triaging transient ischemic attack and acute cerebrovascular syndromes

Jean-Marc Olivot and Gregory W. Albers

Department of Neurology and Neurosciences, Stanford University Medical Center, Stanford Stroke Center, Palo Alto, California, USA

Correspondence to Jean-Marc Olivot, MD, PhD, Stanford Stroke Center, Ste. 205, 780 Welch Road, Palo Alto, CA 94304, USA
Tel: +1 650 7234481; fax: +1 650 7234451; e-mail: jmolivot@stanford.edu

Current Opinion in Neurology 2011, 24:44–49

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

Preliminaries 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

Curr Opin Neurol 24:44–49

1350-7540

Introduction

Ischemic stroke results from the occlusion of an intracranial vessel by a thrombus or embolism. The occlusion of the intracranial vessel induces a local decrease of cerebral blood flow (CBF). A dramatic decrease of CBF can result in brain cell death within minutes [1,2]. This region is called the core of the infarct. It is intertwined with a region called the penumbra where the CBF level is still compatible with transient brain cell survival but cellular function is impaired. Recanalization of the occluded vessel can reverse ischemic cell dysfunction in the penumbra and favors neurological recovery, while a persistent occlusion results in the progressive extension of the core into the penumbra and a worse prognosis [3].

A thrombolytic treatment, recombinant tissue plasminogen activator (rt-PA) administered intravenously within the first 4.5 h after symptom onset is the only intravenous recanalization therapy that has demonstrated clinical benefits in randomized trials [4••,5]. The patients entered in these studies were treated on the basis of a normal head computed tomography (CT) that excludes the presence of acute intracerebral hemorrhage (ICH). After 4.5 h this strategy has failed to identify patients who benefit from treatment [4••]. Nonetheless several studies have demonstrated the persistence of a significant amount of penumbra among many patients after 4.5 h. These findings suggest that many patients can still benefit from an acute recanalization. In contrast, there may be a subset of patients who do very poorly with recanalization therapy even when treated within 4.5 h because of a large amount of early core tissue and limited penumbra.

A transient ischemic attack (TIA) has traditionally been defined as an episode of neurological symptoms of presumed vascular origin that spontaneously resolves in less than 24 h. It results from the spontaneous recanalization of an occluded vessel. TIA diagnosis is retrospective and the agreement on the vascular nature of transient symptoms can be low even among stroke specialists [6•]. TIA is associated with an immediate high risk of disabling stroke that can be prevented by a specialized urgent management [7]. Several factors have been associated with stroke risk following TIA: the clinical characteristics of the patient (age, type and duration of symptoms, blood pressure, diabetes) summarized by the ABCD2 scale [8], the presence of an acute infarction on MRI and a symptomatic neck or brain vessel stenosis [9,10•,11,12•].

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

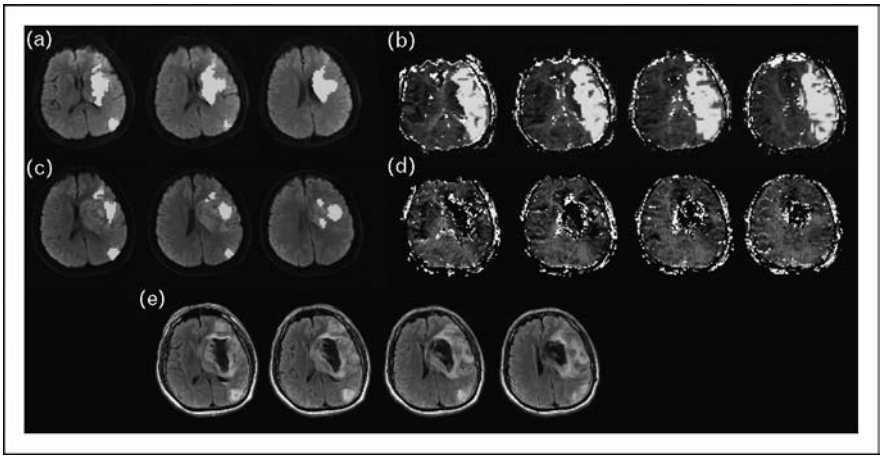
Severe ischemia induces a failure of adenosine triphosphate (ATP) metabolism that leads to the passive influx of water in the intracellular space resulting in cell swelling called cytotoxic edema. The cytotoxic edema decreases the apparent diffusion coefficient (ADC) [15,16]. Acute brain infarction is 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].

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.

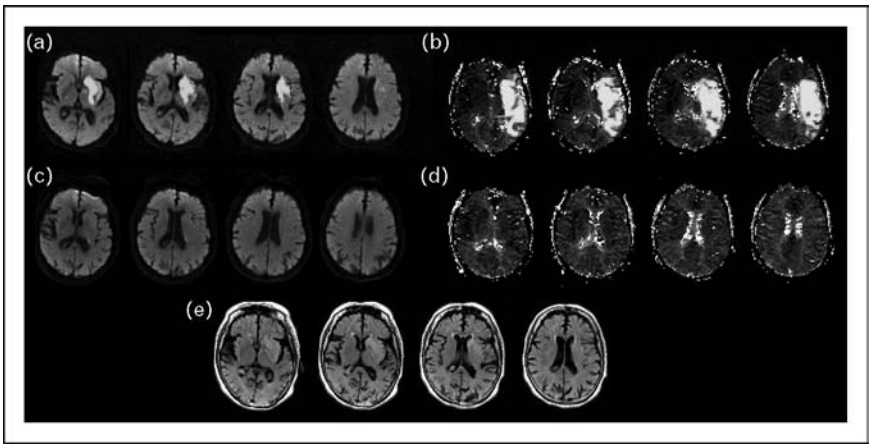
Malignant infarctions are defined as very large infarctions that progress spontaneously to brain herniation and death. A study has suggested that malignant infarctions were associated with DWI lesions larger than 145 cm^3 [18]. Patients with these large acute lesions benefit from emergent craniectomy 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

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_{max} >6 s) of 125 cm^3 (b). The severe perfusion delay (outlined by T_{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.

Figure 2 Eighty-two-year-old female experiencing an acute left middle cerebral artery infarction (National Institutes of Health Stroke Scale score = 22)

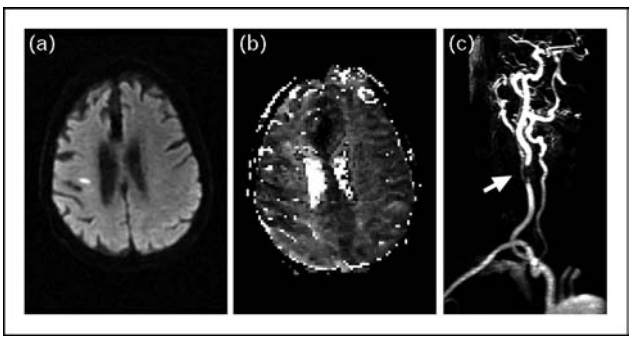


Initial MRI performed 2 h after symptom onset demonstrates a significant mismatch with a diffusion weighted imaging (DWI) lesion of 9 cm^3 (a) surrounded by a large perfusion weighted imaging (PWI) lesion of 83 cm^3 (b). Complete reperfusion demonstrated by a follow-up PWI volume of 0 (d) was achieved and was associated with early DWI lesion reversal (c), and a final infarct on follow-up FLAIR (e), performed at 5 days, that was comparable to the acute DWI lesion volume. National Institutes of Health Stroke Scale (NIHSS) score was 1 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••].

Figure 3 Seventy-five-year-old female experiencing transient left motor deficit



ABCD2 = 4. MRI performed 12 h after symptom resolution revealed an acute infarction in the RMCA territory (a), a T_{max} lesion in the right hemisphere (b), and a tight right internal carotid artery (ICA) stenosis (c), that was successfully treated by endarterectomy the following day.

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_{max} [28,29•]. T_{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_{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_{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_{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_{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_{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 is 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 mutiparametric algorithm to define penumbral tissue. DEFUSE *2* is using a quantitative evaluation of the ADC to determine core and T_{max} more than 6 s 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 4.5–9 h 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].

Acknowledgements

G.W.A. was supported by NIH grant 5R01NS039325 (DEFUSE 2) and a consultant for Genentech and Lundbeck.

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).

1 Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia: the ischemic penumbra. Stroke 1981; 12:723–725.

2 Hossmann KA. Viability thresholds and the penumbra of focal ischemia. Ann Neurol 1994; 36:557–565.

3 Furlan M, Marchal G, Viader F, *et al.* Spontaneous neurological recovery after stroke and the fate of the ischemic penumbra. Ann Neurol 1996; 40:216–226.

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 4.5 h but not after.

5 Hacke W, Kaste M, Bluhmki E, *et al.* Thrombolysis with alteplase 3 to 4.5 h after acute ischemic stroke. N Engl J Med 2008; 359:1317–1329.

6 • Castle J, Mlynash M, Lee K, *et al.* Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. Stroke 2010; 41:1367–1370.
This study illustrates the limitations of the sole evaluation of clinical note to reach an agreement on the vascular nature of transient neurological symptoms.

7 Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2007; 6:1063–1072.

8 Johnston SC, Rothwell PM, Nguyen-Huynh MN, *et al.* Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007; 369:283–292.

9 Purroy F, Montaner J, Molina CA, *et al.* Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. Stroke 2007; 38:3225–3229.

10 • Calvet D, Touze E, Oppenheim C, *et al.* DWI lesions and TIA etiology improve the prediction of stroke after TIA. Stroke 2009; 40:187–192.
This cohort study underlines the role of TIA mechanism and DWI to improve the prediction of future stroke risk.

11 Coutts SB, Simon JE, Eliasziw M, *et al.* Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. Ann Neurol 2005; 57:848–854.

12 • Ay H, Arsava EM, Johnston SC, *et al.* Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model. Stroke 2009; 40:181–186.
This study demonstrates that a restricted diffusion on a patient's MRI performed within 24 h after a TIA was an independent risk factor of early stroke recurrence.

13 Kidwell CS, Chalela JA, Saver JL, *et al.* Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA 2004; 292:1823–1830.

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 the ischemic lesion and its impact on mismatch definition (other references on the subject [40•,41•]).

15 Moseley ME, Cohen Y, Kucharczyk J, *et al.* Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology 1990; 176:439–445.

16 Hossmann KA, Fischer M, Bockhorst K, *et al.* NMR imaging of the apparent diffusion coefficient (ADC) for the evaluation of metabolic suppression and recovery after prolonged cerebral ischemia. J Cereb Blood Flow Metab 1994; 14:723–731.

17 Davis DP, Robertson T, Imbesi SG. Diffusion-weighted magnetic resonance imaging versus computed tomography in the diagnosis of acute ischemic stroke. J Emerg Med 2006; 31:269–277.

18 Oppenheim C, Samson Y, Manai R, *et al.* Prediction of malignant middle cerebral artery infarction by diffusion-weighted imaging. Stroke 2000; 31:2175–2181.

19 Vahedi K, Hofmeijer J, Juettler E, *et al.* Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol 2007; 6:215–222.

20 Selim M, Fink JN, Kumar S, *et al.* Predictors of hemorrhagic transformation after intravenous recombinant tissue plasminogen activator: prognostic value of the initial apparent diffusion coefficient and diffusion-weighted lesion volume. Stroke 2002; 33:2047–2052.

21 Albers GW, Thijs VN, Wechsler L, *et al.* Magnetic resonance imaging profiles predict clinical response to early reperfusion: the Diffusion and Perfusion Imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study. Ann Neurol 2006; 60:508–517.

22 Davis SM, Donnan GA, Parsons MW, *et al.* Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol 2008; 7:299–309.

23 Mlynash M, De Silva DA, Lansberg MG, *et al.* Optimal definition of malignant profile in the DEFUSE-EPITHET pooled database. Stroke 2010; 41:e207.

24 • Yoo AJ, Verduzco LA, Schaefer PW, *et al.* MRI-based selection for intra-arterial stroke therapy: value of pretreatment diffusion-weighted imaging lesion volume in selecting patients with acute stroke who will benefit from early recanalization. Stroke 2009; 40:2046–2054.

The results of this retrospective study show that intra-arterial recanalization is not beneficial for patients experiencing an acute brain infarction outlined by an acute DWI lesion larger than 70 cm^3.

25 Redgrave JN, Coutts SB, Schulz UG, *et al.* Systematic review of associations between the presence of acute ischemic lesions on diffusion-weighted imaging and clinical predictors of early stroke risk after transient ischemic attack. Stroke 2007; 38:1482–1488.

26 •• Easton JD, Saver JL, Albers GW, *et al.* Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009; 40:2276–2293.

In this landmark publication the AHA scientific comitee requalified patients with transient symptoms and a restricted diffusion lesion on MRI as having suffered a brain infarction and recommends acute brain MRI (with DWI) for the initial evaluation of TIA patients.

27 •• Giles MF, Albers GW, Amarenco P, *et al.* Addition of brain infarction to the ABCD2 Score (ABCD2I). A collaborative analysis of unpublished data on 4574 patients. Stroke 2010; 41:1907–1913.

This meta-analysis demonstrates that the incorporation of brain infarction detection on acute brain imaging into the ABCD system improves the prediction of stroke in the acute phase after transient ischemic attack.

28 Kane I, Sandercock P, Wardlaw J. Magnetic resonance perfusion diffusion mismatch and thrombolysis in acute ischaemic stroke: a systematic review of the evidence to date. J Neurol Neurosurg Psychiatry 2007; 78:485–491.

29 • Christensen S, Mouridsen K, Wu O, *et al.* Comparison of 10 perfusion MRI parameters in 97 sub-6-h stroke patients using voxel-based receiver operating characteristics analysis. Stroke 2009; 40:2055–2061.

In this comparative evaluation of perfusion MRI parameters the authors outline the limitations of deconvoluted perfusion maps (such as T_{max}) for the prediction of final infarction.

30 • Calamante F, Christensen S, Desmond PM, *et al.* The physiological significance of the time-to-maximum (T_{max}) parameter in perfusion MRI. Stroke 2010; 41:1169–1174.

This review publication outlines the characteristics and limitations of the T_{max} sequence.

31 • Olivot JM, Mlynash M, Thijs VN, *et al.* Optimal T_{max} threshold for predicting penumbral tissue in acute stroke. Stroke 2009; 40:469–475.

This DEFUSE substudy, suggests that T_{max} thresholds enclosed between 4 and 6 s gave a better prediction of critically hypoperfused brain than the initially predefined T_{max} more than 2 s thresholds used in DEFUSE and EPITHET. This finding concurs with those obtained by a direct comparisom between PWI MRI and PET scan in the pivotal publication of Takasawa *et al.* [32].

32 Takasawa M, Jones PS, Guadagno JV, *et al.* How reliable is perfusion MR in acute stroke? Validation and determination of the penumbra threshold against quantitative PET. Stroke 2008; 39:870–877.

33 • Olivot JM, Mlynash M, Zaharchuk G, *et al.* Perfusion MRI (Tmax and MTT) correlation with xenon CT cerebral blood flow in stroke patients. Neurology 2009; 72:1140–1145.

This study compared back-to-back PWI MRI and Xe-CT among patients with a subacute brain infarction. Its results confirm that T_{max} more than 6 s gave the best measurement of critical hypoperfusion but also showed the limitation of PWI MRI for the quantitative assessment of cerebral hemodynamics.

34 • Kim JH, Bang OY, Liebeskind DS, *et al.* Impact of baseline tissue status (diffusion-weighted imaging lesion) versus perfusion status (severity of hypoperfusion) on hemorrhagic transformation. Stroke 2010; 41:e135–e142.

This publication was one of the first to outline the importance of the size and severity of PWI lesion to predict the risk of hemorrhagic transformation.

35 • Campbell BC, Christensen S, Butcher KS, *et al.* Regional very low cerebral blood volume predicts hemorrhagic transformation better than diffusion-weighted imaging volume and thresholded apparent diffusion coefficient in acute ischemic stroke. Stroke 2010; 41:82–88.

In this EPITHET substudy, the authors demonstrate that severely decreased regional CBV was an important predictor of hemorrhagic transformation.

36 • Mlynash M, Olivot JM, Tong DC, Lansberg MG, *et al.* Yield of combined perfusion and diffusion MR imaging in hemispheric TIA. Neurology 2009; 72:1127–1133.

This study shows that PWI imaging could improve the yield of MRI to detect acute ischemic lesion among TIA patients.

37 Krol AL, Coutts SB, Simon JE, Hill MD, *et al.* Perfusion MRI abnormalities in speech or motor transient ischemic attack patients. Stroke 2005; 36:2487–2489.

38 Perez A, Restrepo L, Kleinman JT, *et al.* Patients with diffusion-perfusion mismatch on magnetic resonance imaging 48 h or more after stroke symptom onset: clinical and imaging features. J Neuroimaging 2006; 16:329–333.

39 Ibaraki M, Ito H, Shimosegawa E, *et al.* Cerebral vascular mean transit time in healthy humans: a comparative study with PET and dynamic susceptibility contrast enhanced MRI. J Cereb Blood Flow Metab 2007; 27:404–413.

40 • Ma H, Zavala JA, Teoh H, *et al.* Penumbral mismatch is underestimated using standard volumetric methods and this is exacerbated with time. J Neurol Neurosurg Psychiatry 2009; 80:991–996.

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

41 • Olivot JM, Mlynash M, Thijs VN, *et al.* Geography, structure, and evolution of diffusion and perfusion lesions in Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE). Stroke 2009; 40:3245–3251.

This DEFUSE substudy confirms the findings of Ma *et al.* [40•] and suggests that these findings may result from an early reperfusion.

42 • Olivot JM, Mlynash M, Thijs VN, *et al.* Relationships between cerebral perfusion and reversibility of acute diffusion lesions in DEFUSE: insights from RADAR. Stroke 2009; 40:1692–1697.

The results of this DEFUSE substudy show that part of the acute DWI lesion is already reperfused (before treatment). This region had a higher reversal rate than the rest of the DWI lesion.

43 • Chemmanam T, Campbell BC, Christensen S, *et al.* Ischemic diffusion lesion reversal is uncommon and rarely alters perfusion: diffusion mismatch. Neurology 2010; 21:1040–1047.

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

44 • Rosso C, Hevia-Montiel N, Deltour S, *et al.* Prediction of infarct growth based on apparent diffusion coefficients: penumbral assessment without intravenous contrast material. Radiology 2009; 250:184–192.

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 nonrecanalizers, and proposed the use of the mismatch between acute infarction and predicted final lesion as a surrogate of the penumbra.

45 •• Hacke W, Furlan AJ, Al-Rawi Y, *et al.* Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion–diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. Lancet Neurol 2009; 8:141–150.

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

46 Campbell BC, Christensen S, Foster SJ, *et al.* Visual assessment of perfusion–diffusion mismatch is inadequate to select patients for thrombolysis. Cerebrovasc Dis 2010; 29:592–596.

47 Davis SM, Donnan GA. MR mismatch and thrombolysis: appealing but validation required. Stroke 2009; 40:2910.

48 Fiebach JB, Schellinger PD. MR mismatch is useful for patient selection for thrombolysis: yes. Stroke 2009; 40:2906–2907.