

Magnetic resonance diffusion-perfusion mismatch in acute ischemic stroke: An update

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Abstract

The concept of magnetic resonance perfusion-diffusion mismatch (PDM) provides a practical and approximate measure of the tissue at risk and has been increasingly applied for the evaluation of hyperacute and acute stroke in animals and patients. Recent studies demonstrated that PDM does not optimally define the ischemic penumbra; because early abnormality on diffusion-weighted imaging overestimates the infarct core by including part of the penumbra, and the abnormality on perfusion weighted imaging overestimates the penumbra by including regions of benign oligemia. To overcome these limitations, many efforts have been made to optimize conventional PDM. Various alternatives beyond the PDM concept are under investigation in order to better define the penumbra. The PDM theory has been applied in ischemic stroke for at least three purposes: to be used as a practical selection tool for stroke treatment; to test the hypothesis that patients with PDM pattern will benefit from treatment, while those without mismatch pattern will not; to be a surrogate measure

for stroke outcome. The main patterns of PDM and its relation with clinical outcomes were also briefly reviewed. The conclusion was that patients with PDM documented more reperfusion, reduced infarct growth and better clinical outcomes compared to patients without PDM, but it was not yet clear that thrombolytic therapy is beneficial when patients were selected on PDM. Studies based on a larger cohort are currently under investigation to further validate the PDM hypothesis.

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Key words: Diffusion; Ischemic; Magnetic resonance imaging; Mismatch; Penumbra; Perfusion; Stroke

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INTRODUCTION

The concept of ischemic penumbra was originally introduced by Astrup *et al*^[1] in 1981, and was defined as an area of reduced cerebral blood flow (CBF) with electrical failure but preserved ion homeostasis and transmembrane electrical potentials. Since then, some other definitions for the ischemic penumbra have been proposed based on energy metabolism, CBF thresholds and protein synthesis^[2]. Because the target of thrombolytic therapy in acute stroke is the brain tissue at risk of infarction, the most clinically relevant definition of the penumbra indicates the ischemic tissue but still viable and salvageable if local perfusion is efficiently restored^[3,4]. It is widely acknowl-

edged that the mismatch of abnormality volume between perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) of magnetic resonance imaging (MRI), has previously and frequently been applied as an imaging equivalent of the ischemic penumbra^[5,6]. The concept of perfusion-diffusion mismatch (PDM) provides a practical and approximate measure of the tissue at risk and has been increasingly applied for the evaluation of acute stroke in animals^[7-10] and patients^[3,4,6,11].

However, this conventional PDM has been challenged^[3,12] by recent studies. It has been evolved into the conviction that PDM does not optimally define the ischemic penumbra. Sufficient data have demonstrated that early abnormality on DWI overestimates the infarct core by including part of the penumbra; and the visible lesion on PWI overestimates the penumbra by including regions of benign oligemia^[4,12-14], in which the mild reductions in tissue perfusion do not actually place the tissue at risk^[4] (Figure 1). This is reflected in clinical results, where the area of final infarction is normally smaller than the maximum perfusion deficit from PWI^[15].

OPTIMAL DEFINITION OF PERFUSION-DIFFUSION MISMATCH

Identification of the PDM is believed to be of considerable therapeutic importance and provides a guideline in patient triage for thrombolytic therapy^[16,17]. However, there exist fundamental controversies in defining a PDM. For instance, there is a lack of consensus regarding what constitute the pairs of mismatch^[18,19] and which PWI-derived parameter best defines the hypoperfused region or predicts lesion growth^[11,19-23].

Some authors suggested that cerebral blood volume (CBV) or CBF is the most reliable parameter to predict final infarct size^[20,24-26]. However, a recent meta-analysis reported varied CBF thresholds for discrimination between infarct core, penumbra and oligemia^[27]. Although it has been accepted by most imaging groups that a parameter from the time domain is the most accurate, there is still no agreement as to which is superior, i.e., time to peak (TTP)^[21,22,28] or mean transit time (MTT)^[11,18,19,29-31]. However, both semiquantitative TTP and MTT tend to overestimate the ischemic lesion volume because of collateral flow^[32,33].

Technically, there are two methods to measure the PDM. One method is to visually rate the PWI-derived parametric maps and DWI as generated by commercial MRI console software. Another method is to quantify the PWI maps and DWI by offline postprocessing based on region-of-interest volumetric calculation. In this quantitative approach, PDM is defined as a ratio of perfusion:diffusion lesion volume of > 1.2 , or as a difference of > 10 -50 mL volumes of abnormality between PWI and DWI^[34-36]. Some researchers considered that qualitative visual evaluation of PDM performed equally with the quantitative PDM measurements. But Campbell *et al.*^[36] reported that the visual assessment of PDM at console

is insufficiently reliable for use in clinical trials due to the great interobserver variability. In addition, Butcher *et al.*^[37,38] found that variability in planimetric PDM measurements arises primarily from differences in PWI volume assessment; because the perfusion-derived readouts may vary greatly due to different examiners and kinetic models applied^[38]. Ma *et al.*^[39] also found that volumetric analysis consistently underestimates the PDM volume. All those mentioned reasons combine to make visual PDM substantially different to quantitative PDM. Better ways are sought to improve the measurement of PDM. These include the semi-automated^[40] or fully automated processing of PDM with dedicated software^[41-43] and the more precise co-registration method for DWI and PWI^[35,39,44].

Although the new concept of PDM has been proposed, currently there is a lack of reliable measures to separate the penumbra part from infarct core on DWI and the benign oligemia from real penumbra on PWI in clinical practice. Many efforts have been made to optimize conventional PDM as described below in order to better define the penumbra.

Serial measurements of perfusion-diffusion mismatch

Since the PDM is strictly time dependent, the moment to acquire PWI is particularly critical in the clinic^[45,46]. It has been shown that the mismatch may exist up to 3 d or even later in patients after symptom onset^[47-51] and most cases of PDM (75%) occurred within the first 6 h after stroke onset in patients^[47]. Recent clinical studies indicated that the presence and extent of reperfusion and collaterals were key factors affecting the evolution of PDM patterns and outcomes of patient with acute stroke^[47,52-56]. Therefore, serial measurements of PDM have been proved to be useful in real-time monitoring of PDM evolution, and might be beneficial for rescuing more stroke patients^[48-50,57,58].

Threshold method for defining perfusion-diffusion mismatch

Recent studies suggested that using a threshold derived from PWI or DWI appeared to provide more accurate discrimination between benign oligemia and penumbra or reversible lesion and infarct core^[27,59-61]. Rohi *et al.*^[62] reported that cutoff values of relative CBF < 0.59 and MTT > 1.63 were optimal in distinguishing the benign oligemia and real penumbra. Oppenheim *et al.*^[63] suggested that the apparent diffusion coefficient (ADC) values best excluded penumbra ($7.82 \pm 0.82 \times 10^{-4}$ mm²/s) from benign oligemia ($8.23 \pm 0.41 \times 10^{-4}$ mm²/s). Prospective investigations are currently undergoing to validate these thresholding techniques with automated software programs^[59].

Other approaches for defining perfusion-diffusion mismatch

Many other approaches have been tried to optimize the definition of PDM. Chen *et al.*^[64] presented initial experiences of utilizing arterial spin labeling PWI in pediatric ischemic stroke patients. Tsang *et al.*^[65] reported that sodium intensity remains unchanged in PDM tissue, indicating preservation of ionic homeostasis. Based on intravoxel

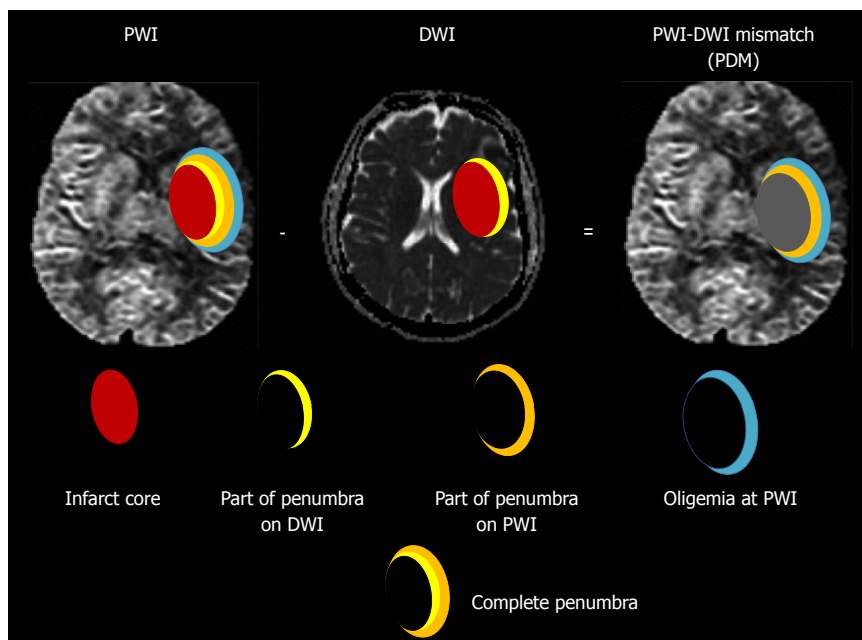


Figure 1 Modern concept of ischemic penumbra. Early abnormality on diffusion weighted imaging (DWI) equals the infarct core plus a part of the tissue at risk (penumbra); and the perfusion deficiency on perfusion weighted imaging (PWI) includes the infarct core plus penumbra and region of benign oligemia. PWI-DWI mismatch (PDM) does not optimally define the ischemic penumbra.

incoherent motion MRI, Suzuki *et al.*^[66] used an independent component analysis, a higher-order statistical signal processing technique, to obtain a perfusion map from a set of diffusion-weighted images based on assumed difference in ADC values. In this way, the PDM can be identified without the PWI data.

POTENTIAL ALTERNATIVES FOR PERFUSSION-DIFFUSION MISMATCH

pH-weighted imaging-perfusion-weighted imaging or diffusion-weighted imaging mismatch

According to Astrup's classic definition of penumbra, the anaerobic metabolism and the formation of lactate lead to a decrease in pH in the area of the penumbra. Sun *et al.*^[67,68] detected the pH-dependent amide proton transfer between endogenous mobile proteins/peptides and tissue water, and obtained pH-weighted imaging (pHWI) during acute ischemia. This modality allowed them to subdivide the PDM into regions with and without tissue acidosis. It was found that the pHWI-deficit area at 3 h was constant during the hyperacute phase of stroke onset; the outer boundary of the hypoperfused area that shows a decrease in pH without DWI abnormality may better correspond to the classic ischemic penumbra area than the PWI deficit. The PWI-pHWI mismatch would then match to benign oligemia, and the pHWI-DWI mismatch to the minimal penumbral area.

Magnetic resonance thermometry-diffusion-weighted imaging mismatch

Elevated temperatures, or pyrexia, in the body or even in brain tissues are common in acute cerebral ischemic stroke^[69,70]. Pyrexia is associated with a worse outcome after stroke, e.g., increased infarct size than normothermia in animal models. In contrast, hypothermia reduced isch-

emic lesion volume on DWI and may improve functional outcome^[71]. Brain temperature (T) can be measured non-invasively with magnetic resonance spectroscopy imaging (MRSI). For each voxel, cerebral temperature can be calculated from the apparent chemical shift of the N-acetylaspartate (NAA) peak, using the following formula: $T = 37\text{ }^{\circ}\text{C} + 100 (\text{NAA}_{\text{peak}} - 2.035)$, where a chemical shift of 2.035 ppm was found in healthy control subjects with an assumed brain temperature of 37 °C. Using this approach, Karaszewski B *et al.*^[71] found that the tissues were hotter in “potential penumbra” (marginally abnormal on DWI or just outside the edge of the DWI lesion) than the “likely infarct core” (definitely abnormal on DWI). The “likely infarct core”, in turn, was hotter than normal brain tissues. Therefore, MRSI provides a promising approach in the study of temperature after stroke and to monitor interventions^[69-71].

Based blood oxygen level-dependent magnetic resonance imaging-based penumbra

This is based on the finding that oxygen extraction fraction (OEF) is significantly increased in the ischemic penumbra^[72]. Deoxyhemoglobin (deoxy-Hb) can be used as an indicator of OEF that can be visualized by T2*-based blood oxygen level-dependent (BOLD) imaging. Geisler *et al.*^[73] applied quantitative T2*-based BOLD imaging (T2') in patients with acute stroke. They found that a signal reduction in the T2' images presumably corresponding with an increase of deoxy-Hb was attributable to an increase of OEF. They also detected shortened T2' values adjacent to the ADC lesion in the region later evolving into infarction, which represents the essential penumbra, and a significant T2' signal loss in the region of a benign oligemia. Therefore, this negative BOLD MRI technique provided an additional metabolic parameter in the better description of the ischemic penumbra^[74,75].

Positron emission tomography-based estimation of penumbra

For positron emission tomography (PET), penumbra was defined as the region with increased OEF and termed “misery perfusion” for this purpose. Normally, cerebral perfusion was assessed by H₂(15)O-PET and tissue damage was estimated by 11C-flumazenil. The determination of absolute values of thresholds for penumbra in patients, however, is difficult since the necessary calculation requires arterial blood sampling. The reported values for the threshold of morphological damage and of the upper limit of penumbra vary considerably (14~22 mL/100 g per minute) by different authors^[72]. Studies demonstrated that PET and PDM were related to the tissue with increased OEF as an indicator of penumbra. PWI was limited in estimating flow and yielded values comparable to H₂(15)O-PET only in the range between 20 and 30 mL/100 g per minute^[76]. In a coregistered PET and DWI study, the characteristic changes of both infarction and penumbra were defined with PET in areas of abnormal DWI^[77,78], with a value of OEF > 150% suggesting the real penumbra^[60].

PET is still considered the gold standard and is the first line technique employed for detection of penumbra and irreversibly damaged tissue, but it is not a readily available methodology^[78,79].

Magnetic resonance angiography-diffusion-weighted imaging mismatch

The magnetic resonance angiography (MRA)-DWI mismatch was defined as an MRA score of 3 (for the intracranial internal carotid artery (ICA) and M1 segment of the MCA, 1 = normal; 2 = reduced flow; and 3 = occlusion) and a DWI lesion volume < 25 mL, or an MRA score of 2 and a DWI lesion volume < 15 mL^[80]. Kim *et al.*^[80] found that the MRA-DWI mismatch was more prevalent in the intracranial large artery atherosclerotic stroke group than in other stroke subtypes. Ma *et al.*^[81] reported that baseline MRA was helpful in categorizing acute ischemic stroke patients into subgroups and should be used in advance of PDM acquisition, because patients may not need thrombolytic therapy if they do not have initial vessel occlusion found by MRA. Another advantage of baseline MRA is the favorable response in patients with arterial occlusion visualized by MRA to increasing doses of thrombolytic agents such as desmoteplase^[82].

Diffusion-weighted imaging - T2W mismatch

It is well accepted that a DWI lesion does not represent the real infarct core because it includes part of the tissue at risk or penumbra. Since the DWI may show initial reduction with no abnormal change on T2W or fluid-attenuated inversion-recovery (FLAIR) images in hyperacute stroke, a DWI-T2W mismatch was proposed to represent the ischemic penumbra. The DWI-T2W mismatch was defined as a hyperintense lesion on DWI (low ADC) with no hyperintense lesion on T2WI or FLAIR, and no hypointense lesion on T1WI. This method may be particularly beneficial to patients with undefined time

windows or beyond 3 h after symptom onset and without PWI data^[83,84].

However, recent progress in DWI suggested that the reversal of the tissue at risk included in DWI abnormality was uncommon in ischemic stroke patients. The volume of reversed lesion on DWI was small and would rarely affect therapy decisions based on PDM theory^[85,86]. Therefore, DWI is generally considered a reliable indicator for predicting ultimate infarction with or without reperfusion^[81,85-89].

Clinical-diffusion mismatch

Since MR-perfusion has limited utilities in many hospitals due to technical reasons^[90], the clinical-diffusion mismatch (CDM) model was proposed as an alternative method for PDM. The CDM is technically less challenging because it does not require PWI^[91]. In order to measure the CDM, Alberta Stroke Programme Early Computed Tomography Score (ASPECTS) methodology was applied to the MRI sequences in an analogous topographical technique as used for computed tomography (CT)^[92]. The CDM was defined as a score of National Institute of Health Stroke Score (NIHSS) ≥ 8 and DWI-ASPECTS ≥ 8 or DWI (lesion volume) ≤ 25 mL. It has been suggested that NIHSS ≥ 8 is a clinical indicator of a large volume of ischemic brain tissue, and had a high rate of early neurological deterioration and lesion growth^[93]. However, there was a discrepancy between CDM and PDM^[94]. Iwanaga *et al.*^[95] found no increased benefit from tissue plasminogen activator (tPA) in patients with CDM, because the positive effects of reperfusion were similar in patients with and without CDM.

Computed tomography-derived mismatch

Infarct core measured on CT was usually segmented based on a CBV threshold of 56% relative to the opposite side. A previous study compared DWI and CBV lesion volumes using thresholds of 46%, 56% and 66% of the contralateral normal side as well as a 2 mL/100 g absolute threshold. The results indicated that the DWI and CBV correlation was optimal using the 56% threshold^[96]. Another study^[97] reported that ischemic penumbra was determined based on a MTT threshold of 150% relative to the contralateral side. Percent volume mismatch was defined as [(MTT - CBV)/CBV] × 100%. In addition to CBV and MTT, some researchers proposed the use of rCBF to calculate the CT mismatch^[98].

Instead of using computed tomography perfusion maps (CTP), Wang *et al.*^[99] suggested the use of CTP source images (CTP-SI) to define a CTP mismatch. Here, the CTP mismatch was defined as a delayed perfusion between arterial phase CTP-SI ASPECTS and venous phase CTP-SI ASPECTS. The presence of such a delayed perfusion can be used as an indicator for thrombolysis.

In a retrospective study, Messé *et al.*^[100] tested a mismatch between ischemic changes on head CT and clinical examination findings (CT-NIHSS mismatch), but his results did not show any correlation between the CT-NIHSS mismatch and MRI PDM.

APPLICATIONS OF PERFUSION-DIFFUSION MISMATCH

The PDM theory was introduced in the late 1990s^[85]. Despite its limitations in imaging ischemic penumbra, this paradigm has been widely used in preclinical research and clinical trials^[16,17]. The PDM model combined with other MRI techniques such as T2WI, FLAIR and MRA have been employed for various purposes^[12].

First, it was used as a practical selection tool for stroke treatment^[101-106]. Only those with appropriate PDM patterns will be enrolled for therapy, like clinical trials of Desmoteplase in Acute Ischemic Stroke Trial (DIAS)^[107], Dose Escalation of Desmoteplase for Acute Ischemic Stroke^[101], and DIAS 2^[104]. However, the results were not repeatable^[82,108-110] in those trials, although better outcomes were found with higher doses of desmoteplase corresponding to the frequency of reperfusion.

Second, to test the hypothesis that patients with PDM pattern will benefit from treatment, while those without mismatch pattern will not, all patients were treated no matter their phases and pretreatment PDM patterns^[112,111]. Clinical trials like The Diffusion and Perfusion Imaging Evaluation For Understanding Stroke Evolution (DEFUSE) and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHEt) were conducted for this purpose. However, the results were not very straightforward. In DEFUSE, no clear pattern of response was found to reperfusion treatment with tPA between patients with PDM and patient without. In EPITHEt, although the infarct growth was smaller in patients treated with tPA, the difference was not statistically significant compared to the controls. Furthermore, the outcomes were better in all patients and PDM patients treated with tPA, but the difference was also not statistically significant^[82,85,101,112].

Third, PDM was applied as a surrogate measure for stroke outcome. Some studies suggested that the abnormality from PWI can be used to predict the lesion growth or final infarct volume^[113-115]. However, this has been challenged due to the evolving PDM concept^[89,116]; because the regions of benign oligemia included in the PWI abnormality did not finally develop into infarction^[4,12,68], and patients without PDM were equally likely to have lesion growth as those with PDM and should also be enrolled in acute stroke treatment^[89,117]. A reduced volume of PDM can be used as an indicator of improvement of stroke severity in a combined anti-stroke study^[89] and of potential for recovery of functions^[118]. Since an acute ischemic lesion was detected with PDM in about 60% of patients with transient ischemic attack (TIA), PDM may play a role in the triage of acute TIA and brain infarction^[118]. PDM can also be applied as an indication for performing interventional procedures like clot removal therapy by aspiration and extraction^[110], urgent carotid artery stenting for acute stroke patients^[108], and transluminal balloon angioplasty for patients with cerebral vasospasm^[109]. In a report by Heidenreich *et al.*^[119] the presumptive treatment plan was changed after PDM-based evaluation in 26% (25/97) of patients with hyperacute stroke. Studies also

revealed that the relation between the anatomic location and PDM may have some indications for the progression or prognosis in patients with hyperacute and acute stroke. For instance, the ischemia stroke was found to progress and have more severe TTP abnormalities in the central part of the MCA territory including the inferior frontal gyrus, superior temporal gyrus, insula, and underlying hemispheric white matter^[120]. The loss of PDM volume (evolving into infarction) was increased in the insula area^[120], and target mismatch was more frequent in the cortex with better outcomes if reperfusion was timely established^[121]. In addition, the severity of leukoaraiosis was associated with the loss of PDM and seems to be a predictor of infarct growth^[122].

MAIN PATTERNS OF PDM AND THEIR CLINICAL RELEVANCE

As the target of thrombolytic therapy of acute stroke, the PDM is normally defined as a mismatch ratio of PWI/DWI ≥ 1.2 , reflecting the presence of clinically significant mismatch^[106,123,124]. However, recent studies suggested the use of a larger ratio of 1.8 to 2.6, because a larger mismatch was associated with a higher response rate in the condition of reperfusion therapy^[125,126].

Although the PWI/DWI mismatch ≥ 1.2 is the predominant pattern in PDM discrepancies^[47], many other PDM patterns have been recently reported and their relevance to subtypes of stroke has not been fully elucidated^[20,47,52,127,128]. Discrepancies between the extent of abnormality on PWI and DWI are supposed to depend predominantly on time from stroke onset to MRI scanning^[45,46,52]. The topographic profiles of these PDM patterns were summarized as follows and in Table 1.

Type I , perfusion-weighted imaging > diffusion-weighted imaging

This pattern is the main type (49%-70%) of PDM and defined as the target mismatch^[125] or positive mismatch^[51] for reperfusion therapy (Figure 2). Bang *et al.*^[125] reported that this pattern is more common in white patients compared with Asian ethnicity with medium-sized lesions on DWI. This pattern was also defined as the classical type of PDM by Ma *et al.*^[121,129], i.e., a DWI lesion within a hypoperfused territory on PWI. In their study, a larger mismatch volume in a cortical location was considered an important factor relevant to the classical pattern, and the presence of distal hyperintense vessels on FLAIR (a potential MRI marker for collaterals) was found to be associated with a large PDM^[130]. But this classic pattern may evolve into a fragmented non-classical PDM pattern over time (up to 48 h), i.e., the dissociation of PWI and DWI lesions. They even found that the types of PDM patterns have little effect on infarct growth, clinical outcomes and the benefit of thrombolytic agent; this suggests that mismatch topography is less important at least during the hyperacute phase of stroke. An animal study also found that the PDM pattern may have evolved over time from

Table 1 Patterns of discrepancy between perfusion-weighted imaging and diffusion-weighted imaging

Pattern	Incidence %	Main etiology	Indications	Potential interventions
I PWI > DWI ^[20,47,51-53,114,121,125,127-130,135] , target mismatch	< 6 h Total 57~86 49~70	Large-artery atherosclerosis, cardioembolism, cryptogenic	Larger lesion on PWI and DWI. Part of tissue at risk and oligemia. Infarct may growth without effective therapy. More common in white patients	Reperfusion therapy: Thrombolytic therapy or angioplasty, stenting
II PWI = DWI ^[20,52,125,131]	~17 ~28	Cryptogenic, large-artery atherosclerosis, cardioembolism, lacunar infarction	No additional tissue at risk. Collateral flow limits the infarct volume to that depicted at DWI. Most common in patients with diabetes	Neuroprotection
III PWI < DWI ^[51,52,114,123,132] , inverse mismatch	~29 6~34	Cryptogenic, cardioembolism, large-artery atherosclerosis, lacunar infarction	Smaller lesion on PWI and DWI. Partial reperfusion may occur at the time of MR scan	Neuroprotection
IV PWI (-), DWI (+) ^[47,114,125]	~8 ~24	Single small MCA branch occlusion, small subclinical infarct	Full reperfusion may occur or due to collaterals at the time of MR scan. More common in Asian patients	Neuroprotection
V PWI (+), DWI (-) ^[47,80,128,133,134] , total mismatch	~8 ~3	Migraine, TIA	Pure perfusion deficit (tissue at risk but not committed to infarction)	Reperfusion therapy
VI PWI (-), DWI (-) ^[20,135]	~14 ~18	Migraine, TIA	No abnormality on both PWI and DWI.	No interventional therapy
VII PWI or DWI > 100 mL ^[82,112] , malignant mismatch		Large-artery atherosclerosis	Normal or hypoperfusion on PET Poor outcome, strongly associated with reperfusion-related brain hemorrhage	Exclusion of therapy

(+): There is abnormality; (-): No abnormality; PWI: Perfusion weighted imaging; DWI: Diffusion weighted imaging; MCA: Middle cerebral artery; TIA: Transient ischemic attack; PET: Positron emission tomography.

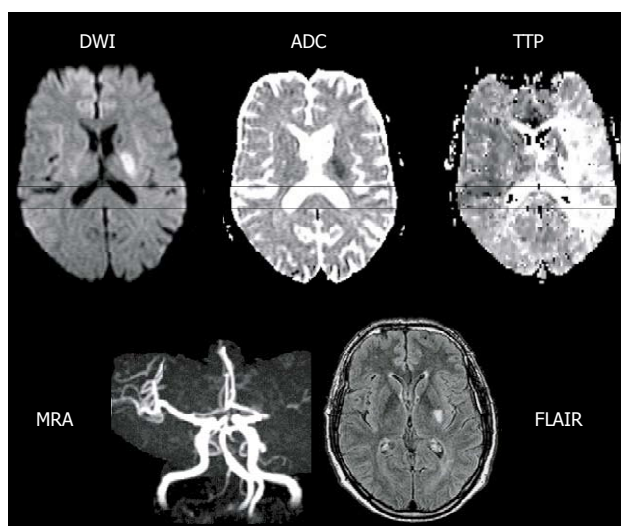


Figure 2 Main pattern of perfusion-diffusion mismatch, perfusion-weighted imaging > diffusion-weighted imaging, in a patient with acute stroke. Extensive area of prolonged time to peak (TTP) and small diffusion-weighted imaging (DWI) lesion in deep middle cerebral artery (MCA) territory, with a complete proximal MCA occlusion on magnetic resonance angiography (MRA) (reprint from Muir KW *et al Lancet Neurol* 2006; 5: 755-68 with permission). ADC: Apparent diffusion coefficient; FLAIR: Fluid-attenuated inversion-recovery.

the so-called classic pattern (PWI > DWI) during initial hours through to a match pattern (PWI = DWI) around 6-12 h to a reverse mismatch (PWI < DWI) at a later time up to 3 d after stroke onset^[51].

Type II, perfusion-weighted imaging = diffusion-weighted imaging

This match pattern means that no additional tissue at risk or penumbra was found, because collateral flow may limit the infarct core evolving into the hypoperfused area on

PWI^[131] (Figure 3). Contrary to that, Bang *et al*^[125] reported that this no target mismatch was the most common type in patients with diabetes. The possible mechanism may be attributed to the early and longstanding hyperglycemia and increased lactate production. All of these may lead to occlusion of small perforators, collateral failure, impaired autoregulation, and consequent loss of penumbra.

Type III, perfusion-weighted imaging < diffusion-weighted imaging

Since the abnormality volume on PWI is smaller than that on DWI, it is considered an inverse or negative mismatch^[51]. The mechanism for this pattern may be attributed to the partial reperfusion which occurred at the time of the MRI scan (Figure 4). Fiebach *et al*^[123] found that this inverse mismatch was frequent in small subcortical ischemic stroke and infarct core may develop beyond the initial hypoperfusion area. In another study, Ma *et al*^[132] found that in 11 of 34 (32%) patients with negative mismatch (PWI < DWI) assessed by the volumetric subtraction technique, all had positive mismatch (PWI > DWI) identified when the more precise coregistration analysis was performed. They named it “hidden mismatch”, which provided an explanation for the previous illogical finding that infarct expansion seems to occur even in the presence of inverse mismatch (PWI < DWI). The “hidden mismatch” observation indicated the possible benefit of treatment for patients even with inverse mismatch^[51,123,132].

Type IV, perfusion-weighted imaging (-), diffusion-weighted imaging (+)

This pattern shows only an infarct lesion on DWI with absence of perfusion deficiency on PWI due to single small artery occlusion or presence of small subclinical

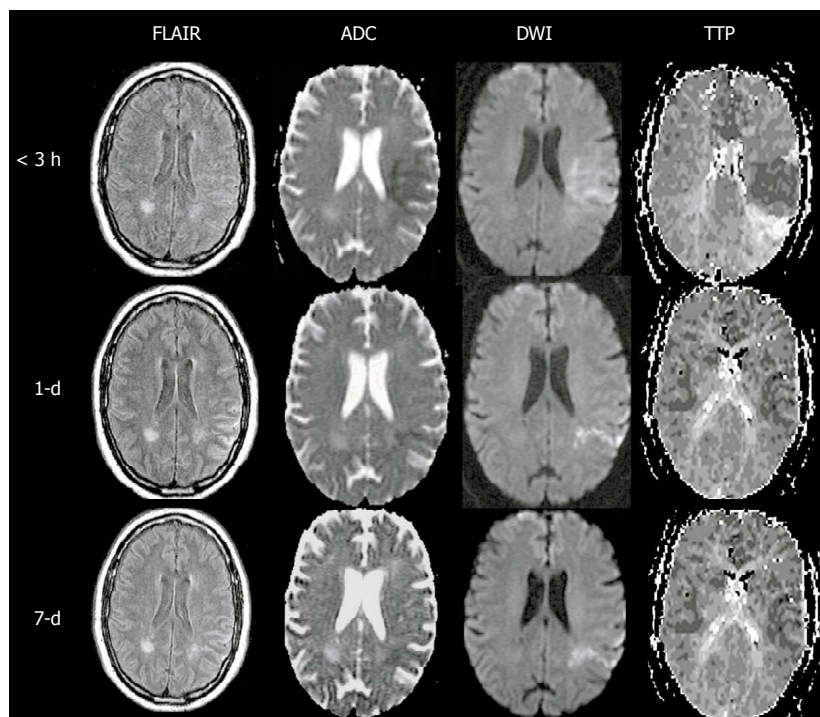


Figure 3 Main pattern of perfusion-diffusion mismatch, perfusion-weighted imaging = diffusion-weighted imaging, in a patient with acute stroke. < 3 h: Fuzzy diffusion-weighted imaging (DWI) lesion in left middle cerebral artery territory matching an area of diminished time to peak, indicating local hyperperfusion and spontaneous recanalization had occurred prior to imaging at 3 h after onset (note the prolonged time to peak at the posterior edge of the DWI lesion, suggesting distal branch occlusion); 1-d: The next day, perfusion has essentially normalized as well as the DWI lesion, save for a narrow posterior streak, suggesting the spontaneous recanalization saved the at-risk tissue from progressing to infarction; 7-d: At day 7, there has been no return of the DWI lesion, indicating the tissue was effectively salvaged (reprint from Muir KW *et al Lancet Neurol* 2006; 5: 755-768 with permission). PWI: Perfusion-weighted imaging; ADC: Apparent diffusion coefficient; TTP: Time to peak; FLAIR: Fluid-attenuated inversion-recovery.

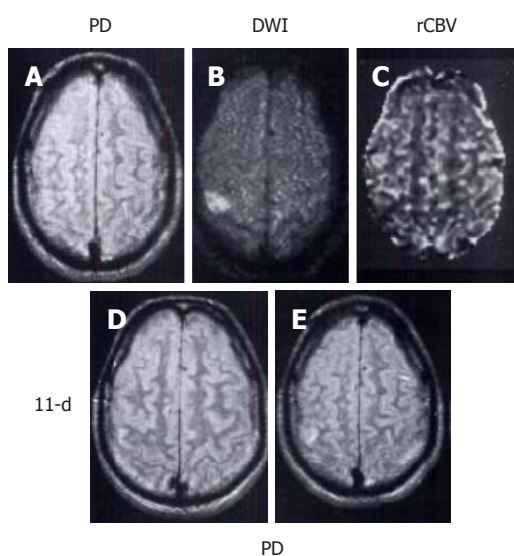


Figure 4 Main pattern of perfusion-diffusion mismatch: perfusion-weighted imaging < diffusion-weighted imaging, in a patient with acute stroke. Patient's left-sided weakness was partially resolved 3 h after the onset of symptoms. A: Proton density (PD) weighted fast spin-echo image shows no abnormality; B: Diffusion-weighted imaging (DWI) shows a focal cortical ischemic abnormality; C: Relative cerebral blood volume (rCBV) map demonstrates a smaller lesion with decreased rCBV compared to the same abnormality as depicted in B; D, E: Follow-up PD images acquired 11 d later show a new tiny hyperintense infarct in the area of initially observed lesion on B and C. Note that the initial DWI lesion is larger than the final infarct volume. The patient's symptoms resolved completely after 2 d (reprint from Sorensen *et al Radiology* 1996; 199: 391-401 with permission).

infarct. This type is more common in Asian patients, because intracranial atherosclerosis and small arterial occlusions were common causes of strokes in Asians and Blacks. Consequently, very small or even absence of the hypoperfusion region was seen in this pattern^[125].

Type V, perfusion-weighted imaging (+), diffusion-weighted imaging (-)

This pattern is also termed total mismatch, i.e. negative DWI and extensive perfusion defects. Recent studies seem to suggest that total mismatch does not necessarily progress to infarction, but may suggest stroke pathogenesis and site of current arterial occlusion. Patients with total mismatch usually have a favorable outcome after recanalization with or without thrombolysis. It also provided evidence of brain ischemia in patients with a clinical diagnosis of migraine or TIA^[80,133,134].

Type VI, perfusion-weighted imaging (-), diffusion-weighted imaging (-)

In this type, there is no abnormality on both DWI and PWI. This pattern was normally found in patients with migraine headaches. Patients' symptoms were associated with localized or "spreading hypoperfusion" along the cerebral cortex as confirmed by PET, and may be resolved completely within 1-48 h^[20,135]. Therefore, the observed hypoperfusion most likely belongs to a type of mild oligemia that cannot even be detected with PWI.

Type VII, perfusion-weighted imaging or diffusion-weighted imaging > 100 mL

The DEFUSE clinical trial defined PWI or DWI volume ≥ 100 mL as a malignant mismatch. A number of studies indicated that patients with the malignant mismatch pattern were more likely to have a poor outcome (modified Rankin Scale score 5 to 6) with reperfusion than without and were strongly associated with reperfusion-related brain hemorrhage due to the severe ischemic brain and microvessel injury. Exclusion of patients with malignant mismatch could improve the safety and efficacy of reperfusion therapies^[82,112].

CONCLUSION

Although the PDM is not yet perfectly matched with the ischemic penumbra, it has been widely recognized as a crude but practical approximation of an imaging equivalent of the pathological ischemic penumbra^[5,6,51]. There is still a lack of consensus regarding the best definition and optimal measurement for PDM. Conclusions draw from recent clinical trials including DEFUSE and EPITHEF suggested that patients with PDM documented more reperfusion, reduced infarct growth and better clinical outcomes compared to patients without PDM^[82,85,125,136,137], but it is not yet clear that thrombolytic therapy is beneficial when patients are selected on PDM^[82]. Studies based on a larger cohort are currently under investigation to further validate the PDM hypothesis^[82]. Given the limitation of current PDM theory, studies in other potential alternatives or imaging biomarkers beyond the PDM concept may help in the management of ischemic stroke patients^[82,85,138].

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