Review Article

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Current concepts on magnetic resonance imaging (MRI) perfusion-diffusion assessment in acute ischaemic stroke: a review & an update for the clinicians

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Recently, several medical societies published joint statements about imaging recommendations for acute stroke and transient ischaemic attack patients. In following with these published guidelines, we considered it appropriate to present a brief, practical and updated review of the most relevant concepts on the MRI assessment of acute stroke. Basic principles of the clinical interpretation of diffusion, perfusion, and MRI angiography (as part of a global MRI protocol) are discussed with accompanying images for each sequence. Brief comments on incidence and differential diagnosis are also included, together with limitations of the techniques and levels of evidence. The purpose of this article is to present knowledge that can be applied in day-to-day clinical practice in specialized stroke units or emergency rooms to attend patients with acute ischaemic stroke or transient ischaemic attack according to international standards.

Key words Acute cerebral infarction - diffusion weighted imaging - emergency medical services - perfusion weighted imaging - stroke

Introduction

Major advances in stroke imaging and treatment, including the Food and Drug Administration (FDA) approval of recanalization therapies for treatment of acute ischaemic stroke (AIS)[1], have led, during the year 2013, to several joint statements by numerous medical societies such as the American Heart Association (AHA), American Stroke Association (ASA), American Society of Neuroradiology (ASR), American College of Radiology (ACR), and the Society of Neuro Interventional Surgery (SNIS), containing imaging recommendations for acute stroke and transient ischaemic attack patients (TIA)[2]. Recent statements by medical societies accept that most stroke patients go untreated and are denied FDA-approved therapies on the basis of hospital arrival time after onset of stroke [3-hour limit for intravenous tissue plasminogen activator (tPA) and 8-hour limit for endovascular clot retrieval][3]. We considered it fitting to present a brief, practical review of current concepts in magnetic resonance imaging (MRI) assessment of AIS, in following with recently published guidelines. The purpose is to introduce the most relevant updated concepts in MRI assessment of AIS that can be applied

in day-to-day clinical practice in formal stroke units or emergency rooms (ER) to attend patients with AIS or TIA according to international standards.

Stroke as a leading cause of death

After years of being the third leading cause of death in the United States, stroke dropped to fourth; this achievement reflected the results of a commitment made by the AHA and ASA more than a decade ago to reduce the incidence of stroke, coronary heart disease, and cardiovascular risk by 25 per cent by the year 2010 (a goal met a year early in 2009)[1].

Incidence of stroke in developed and developing countries

Among developed countries, studies comparing the age-adjusted incidence of stroke between Hispanic and white populations in the USA have shown significant differences in first ischaemic stroke: 140-168 per 100,000 and 88-136 per 100,000, respectively[4]. In European countries, higher incidence rates are reported, with significant differences between genders. Among men of all ages, the incidence of stroke ranged from 124 per 100,000 in South London (2003) to 185 per 100,000 in the Scottish Borders region (1998); among women, the incidence ranged from 88 to 146 per 100,000 in the same studies[5]. The incidence of stroke was similar in studies done in Oxfordshire and East Lancashire, ranging from 135 to 152 per 100,000 among males[5].

Developing countries around the world have reported annual incidence rates (first-ever stroke) of 183 per 100,000 (1995) in Cuzco, Peru; 103.4 cases per 100,000 (2008) in the city of Birjand, Iran; and 89 per 100,000 (1993) in Sabaneta, Colombia[6]. Most of these reports were published from tertiary care hospitals, but an annual incidence of 119 per 100,000 (2013) was reported in a quaternary care hospital in Mexico City, Mexico[7]. Higher incidence rates might reflect an improvement in the awareness of stroke and its signs or symptoms, as well as more feasible and simple accessibility to health care centers, both of which developments might raise the number of patients referred to tertiary/quaternary care hospitals[7].

Clinical and imaging definitions of stroke

The World Health Organization (WHO) definition of stroke, "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin", is still the accepted standard[8]. In the last decade, diffusion-weighted imaging (DWI), an advanced MRI technique, added another dimension to diagnostic imaging, improving the diagnostic yield while being practical and feasible[8]. DWI measures the net movement of water in tissue due to random (Brownian) molecular motion and shows hyperintense ischaemic tissue changes within minutes to a few hours after arterial occlusion due to a reduction of the apparent diffusion coefficient (ADC). This ADC reduction occurs primarily in the intracellular space associated with disruption of membrane ionic homeostasis and cytotoxic oedema. In terms of clinical interpretation, an increased signal on DWI (described in MRI reports as a hyperintense focal region), followed by a decreased ADC map, represents irreversible ischemia, that is, an infarcted brain region; the combination of DWI and ADC maps with T2-weighted images allows to distinguish acute from subacute or older AIS lesions[9]. Fig. 1 shows the imaging findings when distinguishing between acute and subacute stroke using DWI, ADC maps and T2-weighted images.

There is still no true imaging gold standard for acute ischaemic stroke (AIS) established by comparison with neuropathologic findings[10]; in most clinical studies,

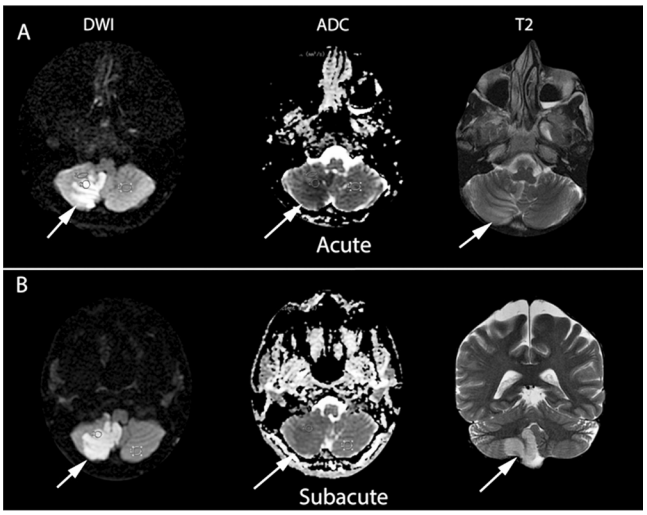

Fig. 1. MRI findings in acute and subacute strokes. **(A)** During acute stroke, infarct regions appear hyperintense on diffusion-weighted imaging, and hypointense on ADC maps (white arrows); they are invisible in T_2-weighted images and Flair during the first 12 h, although some regions of acute infarct might start being noticeable in T_2-w in the 12-24 h period, as in this case. **(B)** Same patient as in A, imaged in the early subacute period; DWI might increase a little. Although the ADC map depicts the return of diffusion values to normal, T_2-w clearly demarcates the extension of the brain infarct (white arrow).

the reference diagnosis of AIS is established using a follow up lesion on computed tomography (CT) or conventional MRI consistent with the clinical syndrome and a comprehensive diagnostic work-up.

Goals in imaging patients with acute stroke

Five basic goals can be pursued in the imaging evaluation of patients with acute stroke symptoms[11]: *(i)* Distinguishing between haemorrhagic and ischaemic stroke; *(ii)* Identifying the location and extent of the intravascular clot; *(iii)* Detecting the presence and extent of the "ischaemic core" (irreversibly damaged tissue); *(iv)* Recognizing the presence of "penumbra" (hypoperfused tissue at risk for infarction); and *(v)* Making an early identification of the aetiology or mechanism of the stroke (*e.g.* carotid atherosclerotic disease, vascular dissection, or other treatable structural causes).

Therapeutic window and imaging evidence for detection of ischaemia

The concept of therapeutic window in the early treatment of hyperacute cerebral ischaemia has changed from the 1995 guidelines, which indicated intravenous therapy from 0 to 3 h or intra-arterial thrombolytic therapy for 4 to 6 h for ischaemic strokes[12]. Current FDA-approved therapies extend the therapeutic window based on hospital arrival time after onset of stroke from 3-hour to 8-hour limits if the maneuver comprises intravenous tPA endovascular clot retrieval respectively[3]. There is strong evidence supporting the use of tPA as a recanalization therapy to improve clinical outcomes during the 0 to 3-hour time window (level 1a) and during the 3 to 4.5-hour time window (level 1b)[13]. Mechanical thrombectomy devices received FDA approval for use in patients arriving at the hospital within 8 h after the onset of symptoms because early recanalization has been found to be associated with a 4- to 5-fold improvement in clinical outcome[14].

The primary goals of imaging during the 0 to 4.5-h time window are to exclude the presence of intracranial haemorrhage and assess the presence and extent of ischaemic changes. The presence of intracranial haemorrhage (excluding microbleeds) is an absolute contraindication to administering intravenous (iv) thrombolytic therapy[11]. MR imaging studies in the acute setting of patients who are potential candidates for iv thrombolysis should not delay administration of iv thrombolysis because"time is brain"[15]; MRI sequences can be often obtained during or following the intravenous administration of tPA.

Diagnostic performance of CT vs MRI in the assessment of stroke patients

Brain and vascular imaging remains a required component of the emergency assessment of patients with suspected AIS and TIA. According to the FDA guidelines for administration of iv thrombolysis, an imaging evaluation, interpreted by a physician with appropriate expertise, should be performed within 45 min of the patient's admission to the emergency department to exclude intracranial hemorrhage[16].

The most recent guidelines accept that the sensitivity and specificity of non contrast CT (NCCT) for detecting intracranial haemorrhage are unknown[11]. The accuracy of MR imaging techniques for detection of intracranial haemorrhage in the acute stroke setting (within 6 h) has been reported as likely equivalent to that of NCCT (level Ib)[17]. In addition, T2*-weighted sequences [including gradient-recalled echo (GRE) and susceptibility-weighted imaging sequences] have greater accuracy in the detection of chronic microhaemorrhages than NCCT[18].

MR-DWI has been found to be more sensitive for detecting ischaemic changes compared with NCCT (level Ia); its sensitivity is reported as 99 per cent with a specificity of 92 per cent[19]. In anterior circulation strokes, the DWI lesion volume correlates well with baseline clinical stroke severity, final infarct volume, and clinical outcome (level II)[20]. There is strong evidence suggesting that MR imaging is superior to NCCT for confirming stroke within the first 24 h (level Ia)[19].

MRI allows the evaluation of the size, location, and vascular distribution of the infarction; the presence of bleeding, the severity of the ischaemic stroke, and/or the presence of large-vessel occlusion; the information about the possible degree of reversibility of ischaemic injury, the intracranial vessel status (including the location and size of the occlusion), and the cerebral hemodynamic status[9]. Additional advantages of MRI compared with CT include its ability to distinguish acute, small cortical, small deep, and posterior fossa infarcts, to distinguish acute from chronic ischaemia, to identify subclinical satellite ischaemic lesions that provide information on stroke mechanism, to avoid exposure to ionizing radiation, and greater spatial resolution[1].

Imaging strategies in AIS

There are three major imaging strategies (and numerous combinations) used in AIS patients

considered for endovascular revascularization therapy, with different underlying rationales and no definitive evidence supporting one strategy over the other[11]: *(i)* Go to the angiography suite immediately after the initial NCCT. The rationale for this approach is to minimize the door-to-recanalization time.

(ii) Obtain a computed tomography angiography (CTA) to assess vascular patency (after NCCT), with or without perfusion imaging, to better characterize the site of occlusion and the ischaemic tissue before making a decision about endovascular treatment.

(iii) Use MR imaging, with DWI and perfusion weighted imaging (PWI), supplemented by MR angiography (MRA), in institutions where it can be performed quickly and on a 24/7 basis.

The choice of imaging strategy may depend on physician's preference and logistical factors. The rationale for the third strategy is that the extra time needed to perform this imaging protocol is compensated by the information gathered and its implications for decision-making[21,22]. Furthermore, some studies have demonstrated that the extra time for imaging until treatment does not adversely affect the outcome[9,23]. An algorithm of the imaging strategies in brain ischaemia based on the availability of CT and/or MRI is presented in Fig. 2.

MRI protocol in the assessment of brain ischaemia

The most commonly used sequences in acute stroke MRI include: DWI, PWI, T_2-weighted imaging, fluid-attenuated inversion-recovery imaging (FLAIR), T_2*-weighted gradient-echo imaging with susceptibility-weighted imaging, and MR angiography[24]; these sequences may require an acquisition time of up to 20 min, allowing for another 25 min for the radiologist´s interpretation, in agreement with the FDA's recommendation of 45 min in patients who are candidates to receive endovascular therapy. Table I shows the acquisition times for each of the sequences in stroke imaging protocols using a 1.5 or 3.0 Tesla scanner; Fig. 3 shows the DWI, PWI and MR angiography images included in a comprehensive evaluation of a patient with acute stroke.

Importance of the identification of penumbra

The presence of an ischaemic penumbra defines the amount of brain tissue at risk of infarction that can be potentially salvaged byearly reperfusion[25]; in other words, the presence of a perfusion-diffusion mismatch

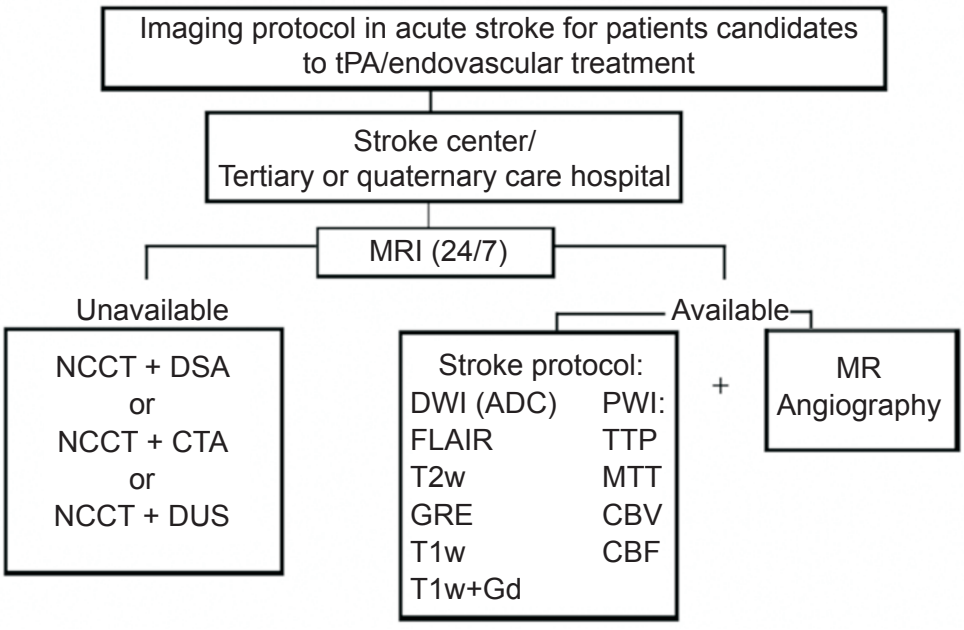

Fig. 2. Imaging strategies in brain ischaemia based on the availability of CT and/or MRI.tPA, tissue plasminogen activator; NCCT, non-contrast computed tomography; DSA, digital subtraction angiography; CTA, computed tomography angiography; DUS, Doppler ultrasound; TTP, time to peak; MTT, mean transit time; CBV, cerebral blood volume; CBF, cerebral blood flow; T1W, T1 weighted imaging; GRE, gradient ecoimaging; PWI, perfusion weighted imaging; FLAIR, fluid-attenuated imaging recovery.

Table I. MRI protocols for acute stroke. Approximate acquisition times using conventional parameters are calculated for 1.5 and 3.0 Tesla scanners

Sequence	3.0 Tesla	1.5 Tesla
Localizer	16 sec	8 sec
Calibration	6 sec	12 sec
Diffusion-weighted imaging (DWI)	59 sec	66 sec
Fluid-attenuated inversion recovery (FLAIR, axial)	177 sec	168 sec
T_2*-weighted gradient-echo	274 sec	394 sec
3D Time-of-Flight	68 sec	68 sec
Perfusion-weighted imaging (PWI)	36 sec	75 sec
Post-gadolinium T_1-weighted imaging	120 sec	100 sec
MR angiography (extracranial carotid arteries)	4.5 min	6 min
Total time	17.1 min	20.85 min

Source: Ref. 46

is a qualitative marker for potential infarct expansion[26]. The DEFUSE[22] and EPITHET[27] clinical trials showed that more than 50 per cent of patients presenting with an acute stroke 3-6 h after onset had an ischaemic penumbra, which was defined as a perfusion volume abnormality at least 20 per cent and 10 ml greater than the diffusion volume abnormality. The results of these two trials showed that a perfusion-diffusion mismatch could be used to select patients for intravenous PA treatment beyond the 3-h window[25].

Although ischaemic penumbra is thought to represent the volumetric difference between the diffusion and perfusion abnormalities, commonly referred to as the diffusion-perfusion mismatch, but recent data have led to a reconsideration of this concept, as not all diffusion abnormalities necessarily result in infarction and the possibility also exists that the perfusion abnormality may represent areas of benign oligemia[28,29].

Basic concepts for the clinical interpretation of diffusion

Because standard MRI sequences (T_1-weighted, T_2-weighted, and FLAIR) are relatively insensitive to the changes of acute ischaemia[30], DWI has emerged as the most sensitive and specific imaging technique for acute infarct, far better than NCCT or any other MRI sequence. It has high sensitivity (88 to 100%) and specificity (95 to 100%) for detecting infarcted regions, even at very early time points[31], within minutes of the onset of symptoms[32]. DWI allows to identify lesion size (even in small cortical lesions), site (deep or subcortical lesions) and age, as well as areas in the brain stem or cerebellum, often poorly or not visualized with standard MRI sequences and NCCT[33]. There are some articles describing negative DWI studies when cerebral perfusion decreased enough to produce infarction[34], as well as the reversal, partial or complete, of DWI abnormalities when perfusion was restored[35]. Thus, early after the onset of ischaemia, the visible diffusion lesion includes regions of irreversible infarction, associated with more severe ADC changes, and regions of salvageable penumbra, associated with less severe ADC changes.DWI-positive lesions tend to be smaller and multiple in TIA patients; these findings are associated with a higher risk of recurrent ischaemic events[36].

Importance of volume measurements in stroke

The critically hypoperfused tissue also known as "core" is the acutely ischaemic brain tissue likely to be irreversibly infarcted even at very early times post ictus, regardless of the physiological basis of the imaging modality used for its detection[9]. The use of image post-processing software makes it possible to report the core volume in cm^3 with unenhanced CT (hypoattenuation), DWI (suggesting severe cytotoxic oedema), FLAIR or T2-weighted MR imaging (hyperintense signal suggests vasogenic oedema).

According to the European Cooperative Acute Stroke Studies (ECASS), a "large" core volume is considered to be one-third of the volume of the middle cerebral artery territory or larger, or approximately 70-100 ml[32]. Some authors have observed that early signs of ischaemia involving more than one-third of the middle cerebral artery territory in the 0 to 6 h time

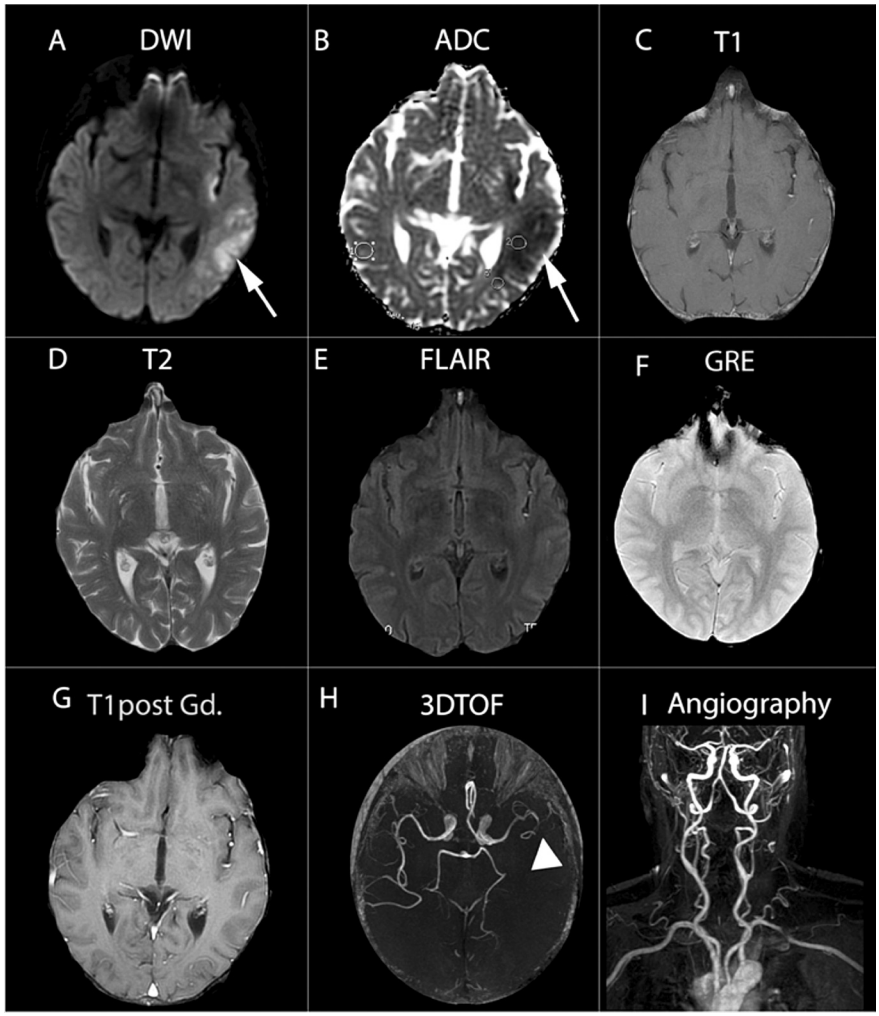

Fig. 3. Comprehensive MRI assessment in acute stroke using DWI, PWI and MR angiography. Selected images depict an acute ischaemic infarct (white arrows), which is visible only in **A**, the diffusion-weighted imaging (DWI); **B**, the apparent diffusion coefficient map (ADC); and **H**, the three-dimensional time-of-flight (3D-TOF); in this last sequence, a white arrowhead (image 3H) indicates the occlusion of the M2 segment in the left middle cerebral artery. The rest of sequences in the protocol: **C**, T1; **D**, T2 weighted images; **E**, Flair; **F**, gradient-echo imaging (GRE); **G**, T1 post gadolinium administration; and **I**, carotid-artery MR angiography did not depict conspicuous findings.

window have been associated with large infarcted regions, increased risk of hemorrhagic transformation and poor outcomes, and thus constitute a relative contraindication to iv thrombolysis[37]. In another report, no patient with a lesion greater than 70 cm^3on DWI at admission had a good outcome[32]. A large volume of "core" tissue is considered as a contraindication to both intravenous and endovascular treatment[38].

Basic concepts for the clinical interpretation of perfusion

Perfusion refers to the delivery of blood to a tissue or organ; brain perfusion is also termed cerebral blood flow (CBF) and is expressed in units of ml/g/min, reflecting the volume of flow per unit brain mass per unit time. Absolute quantification of CBF requires a tracer that can diffuse from the vasculature into tissue. The intravascular (non diffusible) and diffusible tracers used by the various methods of PWI do not quantify CBF with precision; however, the haemodynamic measurements done with them are often referred to as perfusion imaging[39].

There are three methods for measuring perfusion with MRI:

Dynamic susceptibility contrast perfusion magnetic resonance imaging (DSC-MRI) relies on the measurement of the T_2-weighted (T_2-w) or T2* decrease

during the first pass of an exogenous endovascular tracer through the capillary bed[40]. DSC-MRI has become the imaging method most commonly distributed by the major MRI vendors and the most frequently used; some related technical aspects are: the duration of the gradient-echo (GRE) sequence is about 1 min and whole brain coverage can be achieved (up to 24 slices)[41]. The tracer used is a conventional chelate of gadolinium, injected through an 18G catheter into a peripheral vein at a regular dose of 0.1 mmol/kg for GRE or 0.2 mmol/kg for spin echo (SE) sequences, and at an injection rate of 5 to 10 ml/sec, immediately followed by a 20-30 ml saline flush. DSC-MRI does not expose patients to ionizing radiation, and intolerance to gadolinium chelates is very rare. However, it has contraindications: pacemakers and some other implanted metallic or electronic devices, obesity (more than 150 kg), fixed ferromagnetic dental devices and intracranial clips, which generate prominent artifacts, and claustrophobic or agitated patients, who may require sedation[42]. DSC-MRI remains the standard approach for perfusion MRI in the brain[43].

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a steady-state T_1-weighted (T_1-w) technique not commonly used due to the fact that the T_1-w technique yields a slightly lower signal-to-noise ratio, and the kinetic modelling algorithms for the estimation of blood volume and vascular permeability are more complex. DCE-MRI remains the method of choice for permeability MRI and has replaced DSC-MRI as the standard approach for perfusion MRI outside the brain[43].

Arterial spin labelling (ASL) uses magnetically labelled arterial blood water as a diffusible flow tracer[39]. Although ASL offers some significant advantages such as no need for contrast media (endogenous brain water is used as a tracer), the ability to perform multiple repeated measurements and to generate perfusion maps of the entire brain, ASL techniques have not achieved widespread clinical usage. This could be partly due to some technical limitations: atypical acquisition lasts between 5 and 10 min depending on the scanner quality (magnetic field, RF coil sensitivity, *etc*.)[42]; ASL cannot accurately map blood flow below ~10ml/100g/min: on the other hand, as flow increases (>150ml/100g/min), ASL will underestimate blood flow[44].

Parametric maps of brain perfusion

By using DSC-MRI, it is possible to calculate parametric maps derived from the time-intensity curves measured in each pixel, representing the four most common parameters assessed in AIS: time-to-peak (TTP), mean transit time MTT (MTT), cerebral blood volume (CBV) and cerebral blood flow (CBF). TTP and MTT are time-dependent maps; TTP corresponds to the delayed bolus arrival time in areas of hypoperfusion, while MTT represents the first moment of the curve. The CBV is estimated from the area under the signal intensity-time curve, and the CBF is proportional to the amplitude of the signal intensity-time curve, which is equal to CBV/MTT[45].

TTP has been found to be the most accurate PWI biomarker for distinguishing penumbra from hyperacute stroke (0-6 h) and acute stroke (7-12 h)[46]. CBV maps correlate best with the final infarct volume, implying that CBV maps incorporate flow via collateral vessels and provide a snapshot of cerebrovascular reserve[25]. In recent and larger studies, relative CBF was found to be more predictive of the ischaemic core (non viable tissue) than CBV[47].

These maps do not afford quantitative assessment of brain haemodynamics, but can be interpreted semi-quantitatively by calculating the ratio or difference between the values in a region of interest (ROI) placed in the abnormal area and a mirror ROI placed in the contralateral area considered as a normal reference[42]. So far, there is a lack of standardization of perfusion imaging acquisition, post-processing, threshold values, and interpretation criteria[38].

Some technical considerations of PWI

When using DSC perfusion maps, low perfusion values can be accurately measured until 8 ml/min/100 g. Under this level, the signal-to-noise ratio becomes too low for a precise quantification; the reproducibility of the method ranges between 10 and 15 per cent[48]. DSC has no age limitation and can be performed in children[42].

A double injection of contrast medium has been proposed for stroke protocol[49], using a double injection protocol with two times 0.05 mmol/kg gadobutrol (gadolinium-based contrast agent) at 3 ml/sec for MRA and 5 ml/sec for perfusion with 20 ml saline flush each. MRA is performed before DSC imaging to avoid influences from circulating contrast media[25].

PWI profiles based on CBV and CBF measurements

Some perfusion profiles have been proposed in the last few years[38,50,51]:

Table II. Recently proposed perfusion profiles in acute stroke imaging

Profile	Cerebral blood flow	Cerebral blood volume	Clinical interpretation
Misery profile	Decreased	Increased	Observed in ischaemic territories with poor collateral flow.
Luxury profile	Increased	Normal	Represents the relative hyperemia of critically ischaemic tissue following recanalization of regions with tissue acidosis.
Malignant profile	Decreased	Decreased	Represents a state of near-zero perfusion; it is the usual finding in the "core" region.

Source: Refs 38, 50, 51

(i) Misery profile (decreased relative rCBF with increased rCBV), observed in ischaemic territories with poor collateral flow.

(ii) Luxury profile (increased rCBF with normal rCBV), representing the relative hyperemia of critically ischaemic tissue following recanalization of regions with tissue acidosis.

(iii) Malignant profile or near-zero perfusion (decreased rCBV and rCBF), the usual finding in the "core" region.

Table II shows the flow and volume patterns of MRI perfusion profiles. Fig. 4 presents the PWI-curves, CBV and CBF maps corresponding to each of the perfusion profiles.

PWI beyond characterization of stroke

There are several applications of PWI beyond characterization of the penumbra and triage of patients to acute revascularization therapy: *(i)* Improve the sensitivity and accuracy of stroke diagnosis[46]; *(ii)* Exclude stroke mimics[52]; *(iii)* Perform a better assessment of the ischaemic core and collateral flow[11]; and *(iv)* Predict haemorrhagic transformation and malignant oedema[53].

FLAIR sequence as alternative for penumbra imaging

Some phase II clinical trials have been conducted to establish the safety of intravenous tPA for strokes of unknown onset time by using the FLAIR-DWI mismatch for patient selection - with DWI being more sensitive to early (>3 h) cytotoxic edema and FLAIR being more sensitive to later (typically >6 h) vasogenic oedema[54,55].

Intracranial haemorrhage

When intraparenchymal haemorrhage is present, as in 15 per cent of all strokes, the imaging evaluation in AIS may include angiography of the intracranial arteries for evaluation of an underlying vascular malformation[56]. The accuracy of MR imaging techniques for the detection of intracranial haemorrhage in the acute stroke setting (within 6 h) has been reported as likely equivalent to NCCT (level Ib)[17]. In addition, T2*-weighted sequences (including GRE and susceptibility-weighted imaging sequences) have greater accuracy in the detection of chronic microhaemorrhages[17]. No significant increased risk of symptomatic haemorrhage has been observed when patients with a small number of chronic microhaemorrhages (< 5) are treated with iv thrombolysis (level Ia)[57].

Stroke mimics

Stroke mimics have been identified in 3 per cent[58] to 21 per cent[59] of several series of patients treated with fibrinolytics. The main causes of stroke mimics are psychogenic (conversion disorder), seizures, hypoglycaemia, migraine with aura (complicated migraine), hypertensive encephalopathy, Wernicke's encephalopathy, central nervous system (CNS) abscess, CNS tumour, and drug toxicity[1]. In suspected stroke, clinicians should use an assortment of clinical evidence, and radiologists need to be on alert for identifying neuroimaging-negative cerebral ischaemia on DWI and PWI in order to distinguish AIS from haemorrhagic stroke and TIA. Expertise in the differential diagnosis of this condition is needed to manage the patients at the point of referral, discarding the most frequent non-stroke diagnoses. A recent systematic review reported seizure, syncope, sepsis, migraine and brain tumours among the most frequent mimics[58].

Limitations for the generalized clinical implementation of MRI assessment

The need for a good MR technician (MRI technologists) with expertise on the production and interpretation of MR images and trained radiologists (interpretation of data), as well as patient compliance

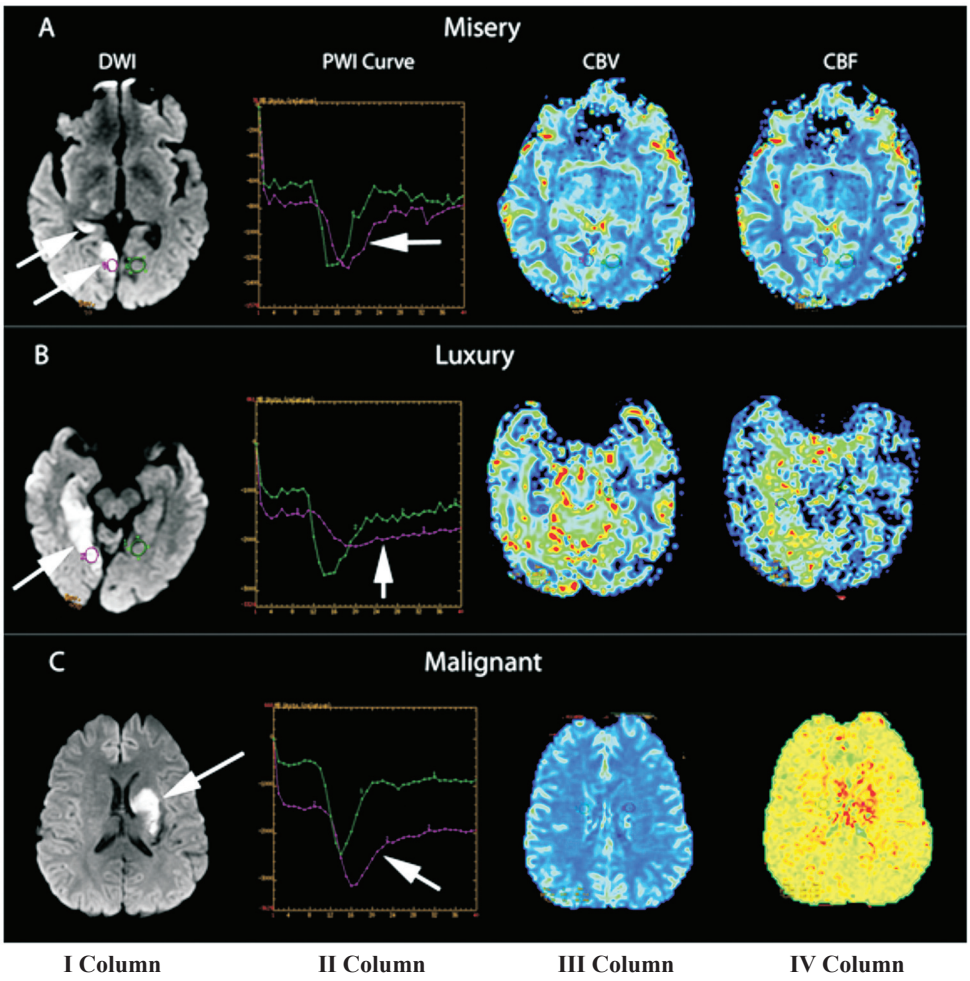

Fig. 4. Diffusion-Perfusion analysis in acute ischaemic stroke. **I column**, location of the infarct core using diffusion weighted imaging (selected ROI is indicated by a small white oval shape); **II column**, perfusion-weighted imaging (PWI) profiles with their corresponding perfusion curves of cerebral blood volume (CBV) and cerebral blood flow (CBF); **III** and **IV columns**, CBV and CBF parametric maps of brain perfusion.

are serious limitations for a generalized use of MRI in AIS. Other limitations of MRI in the acute setting include cost, the relatively limited availability of the test, the relatively long duration of the test, increased vulnerability to motion artifact, and patient contraindications such as claustrophobia, cardiac pacemakers, patient confusion, or metal implants; in addition, in up to 10 per cent of patients, an inability to remain motionless may prevent the ability to obtain a quality MRI[1]. However, despite all these logistical issues that limit the use of MR imaging in the emergent setting, recent statements from many facilities around the world favour the performace of brain MRI in patients with uncertain clinical diagnosis or in centers where MR imaging is readily available all the time; they also favour streamlined protocols that limit imaging time to the standard-of-care guidelines for thrombolytic therapy[11]; these centers include tertiary and quaternary care hospitals, and some stroke centers. In these facilities, MRI, including DWI, is the preferred brain diagnostic imaging modality; if MRI is not available, head CT should be performed (Class I; Level of Evidence B)[1].

CT perfusion as an effective imaging modality in AIS

Although CT or MRI may be used as the initial imaging test, and MRI has been recognized as more sensitive to the presence of ischaemia, in most institutions CT protocols remain the most used initial brain imaging. There is growing consensus for using CT perfusion (CTP) with the latest generation CT units, as well as digital subtraction angiography (DSA) and DSA perfusion. In certain situations where MR is

not available, CTP is an effective imaging modality for diagnosis and treatment decisions in acute stroke[61].

Conclusions

There are advantages in the use of diffusion-perfusion MRI rather than NCCT in clinical practice only in the context of tertiary and quaternary care hospitals where MR imaging is readily available. The caveat of using current perfusion techniques is that there is still no consensus about their use fullness for reliably identifying the penumbra. Further studies are needed to reach consensus about nomenclature, conceptual issues, and measurement errors; cost-benefit issues should also be addressed by appropriate medical-economic protocols.

An imaging technique does not require level A evidence to be considered "non-investigational" or "medically necessary"[1]. Integration of clinical and laboratory data with DWI, PWI and MRA, as part of a global MRI protocol for stroke, would allow clinicians to determine with reasonable certainty whether the patient's clinical deficits can be explained by infarcted tissue.

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