CASO QUIZ

Usefulness of diffusion-perfusion analysis by magnetic resonance imaging for ischemic penumbra detection in brain stroke

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Resumen

El accidente cerebrovascular es la principal causa de mortalidad y morbilidad en el mundo desarrollado. El avance tecnológico actual permite no sólo una representación del tejido infartado, sino también de los tejidos adyacentes con oligemia, es decir, la región de la penumbra. Se considera que la resonancia magnética (RM) es el mejor método para el estudio y evaluación de infarto cerebral y la penumbra. En la actualidad, imágenes convencionales son sólo un complemento en el análisis de difusión-perfusión, permiten cuantificar el flujo sanguíneo cerebral y el volumen (CBF y CBV), así como el tiempo-a-pico (TTP) tras la administración de contraste. Estos tres parámetros constituyen las variables hemodinámicas que se alteran en un infarto cerebral. En este trabajo se presentan los hallazgos típicos de la RM en el caso clínico de un paciente con infarto cerebral hiperagudo que muestra la pérdida de flujo sanguíneo de la arteria cerebral media, una importante zona de penumbra, disminución de ADC de 40 a 70%, disminución de la CBF y CBV, aumento de MTT, y TTP con retraso de 10 a 13 s.

Palabras clave. Accidente vascular cerebral. Penumbra. Isquemia. Difusión. Coeficiente de difusión aparente. Perfusión. Resonancia magnética nuclear.

Abstract

Stroke is the leading cause of mortality and morbidity in the developed world. Current technological advancement allows not only a depiction of the infarcted tissue, but also of the adjacent tissue with oligemia, i.e., the region of penumbra. We consider that magnetic resonance (MR) imaging is the best method for the study and assessment of brain stroke and penumbra. Conventional imaging is currently only a complement to the diffusion-perfusion analysis that allows us to quantify cerebral blood flow and volume (CBF and CBV), as well as the time-to-peak (TTP) following the administration of contrast material. These three parameters constitute the hemodynamic variables that are altered in a brain stroke. In this paper we present the typical MR findings in the clinical case of a patient with hyperacute brain stroke, showing blood flow loss from the left middle cerebral artery, an important area of penumbra; ADC decrease from 40 to 70%; CBF and CBV decrease; MTT increase, and TTP with a delay of 10 to 13 s.

Key words. Cerebral vascular accident. Penumbra. Ischemia. Diffusion. Apparent diffusion coefficient. Perfusion. Magnetic resonance.

INTRODUCTION

Stroke can be defined as an acute central nervous system injury with an abrupt onset. According to the World Health Organization (WHO), stroke is the fast development of clinical signs of disturbance in the cerebral functions, with symptoms that persist during 24 h or more and that can lead to death, showing no other evident cause than a vascular origin. Acute cerebral ischemia constitutes approximately 80% of all stroke cases and is an important cause of morbidity and mortality in the United States.[1]

In Mexico the high prevalence of arterial hypertension and diabetes mellitus among the population makes stroke

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the sixth general cause of death, ranking fourth place for female mortality and sixth place for male mortality.[2]

The aim of evaluating acute or chronic stroke by MR imaging is detecting salvageable cerebral tissue (indicated by a penumbra that surrounds the infarcted area on the brain images of the patient) so that the radiologist can inform of such findings in a written report. This has led to the development of functional MR imaging techniques, such as cerebral perfusion images. In 2001, Dr. Rowley[3] proposed four points that the imaging report of a patient with acute stroke should include: brain parenchyma; the pipes (arteries) that conform the Willis polygon (as well as the assessment of extracranial circulation, in the same evaluation); quantitative data of cerebral perfusion; and the detection of whether an area of penumbra exists or not in the diffusion-perfusion analysis (Table 1). This approach enables the localization and description of intracranial hemorrhage, the identification of intravascular thrombi, the differentiation of infarcted tissue from salvageable tissue, the selection of a corresponding therapy, and the prediction of clinical outcome.[4]

The definition of penumbra in MR imaging has been described in simple terms as the mismatch between the areas of infarcted tissue (observed in the diffusion parameters) and the areas of ischemic tissue (evaluated in the perfusion parameters).[5] A significant operational mismatch between the diffusion and perfusion parameters is settled when the values have over 20% of discrepancy, a finding that suggests that an expansion of the infarcted area is likely to occur when the ischemic area on perfusion sequences is larger than the infarcted area on the initial diffusion sequences. Such difference in area or volume represents the concept of ischemic penumbra.[5] We present the typical findings of the diffusion-perfusion analysis by MR in a case of ischemic stroke with a penumbra, along with a brief review of the literature.

CASE REPORT

A 70-year-old female patient with a history of abrupt onset of unstable walking and weakness of the right limbs attended the ER room of our medical facility within the first hours of presenting the described symptoms; the cross-examination reported a pathological background of rheumatic heart disease with double mitral lesion, moderate mitral and aortic insufficiency, partial gastrectomy and vagotomy in 1998, as well as cardiac catheterization 10 days before the ischemic event. The neurologic exploration confirmed ataxia and right facio-corporal hemiparesis of brachial predominance, right pyramidal syndrome, and motor aphasia.

Based upon the exploration results, an evaluation of the brain by computed tomography (CT) was performed, with the following findings: hyperdense left middle cerebral artery (MCA) and mild left temporal edema with mild displacement from the middle line. These findings were suggestive of penumbra, therefore prompting the treating neurologist to request a MR evaluation with the aim of determining whether there was any salvageable tissue (indicated by the presence of the penumbra) and initiate therapeutic maneuvers.

On diffusion-weighted sequences and at the quantitative post-processing of their apparent diffusion coefficient (ADC), the MRI assessment revealed two hyperintense focal images (measuring less than 2 mm) with a tendency to confluence; one of them was localized in the left thalamus, and the other was located towards the semi-oval center (Figures 1A, 1E). These lesions were not observed on conventional FLAIR, gradient-echo, and contrast-enhanced T1-weighted sequences (Figures 1C, 1D, 1F).

At diffusion post-processing, the ADC showed decreased diffusion, ranging from 42 to 70%, with stronger severity in the thalamus region (Figure 1B). Post-processing of the perfusion sequence reported an important area of penumbra that was larger than the area corresponding to diffusion. Semi-quantitative measurement of cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT), showed an increase, with values of 202, 148 and 103%, respectively. The time-to-peak (TTP) had a major delay of 10-13 s. The graphic representation of perfusion displayed a classic curve of smaller size with a deviation to the right, compared with the perfusion curve of healthy cerebral tissue (Figure 2A-2F).

The sequence that assessed intracranial vessels (3DTOF) showed an interruption of the blood flow from the M1 segment of the left middle cerebral artery (MCA);

Table 1. Goals of Acute Stroke Imaging, modified from Rowley, *et al.*[3]

Parenchyma	Assess early signs of acute stroke; rule out hemorrhage.
Pipes	Assess extracranial circulation (carotid and vertebral arteries of the neck) and intracranial circulation for evidence of intravascular thrombus.
Perfusion	Assess cerebral blood volume, cerebral blood flow, mean transit time, and time-to-peak.
Penumbra	Assess tissue at risk of dying if ischemia continues without recanalization of intravascular thrombus.

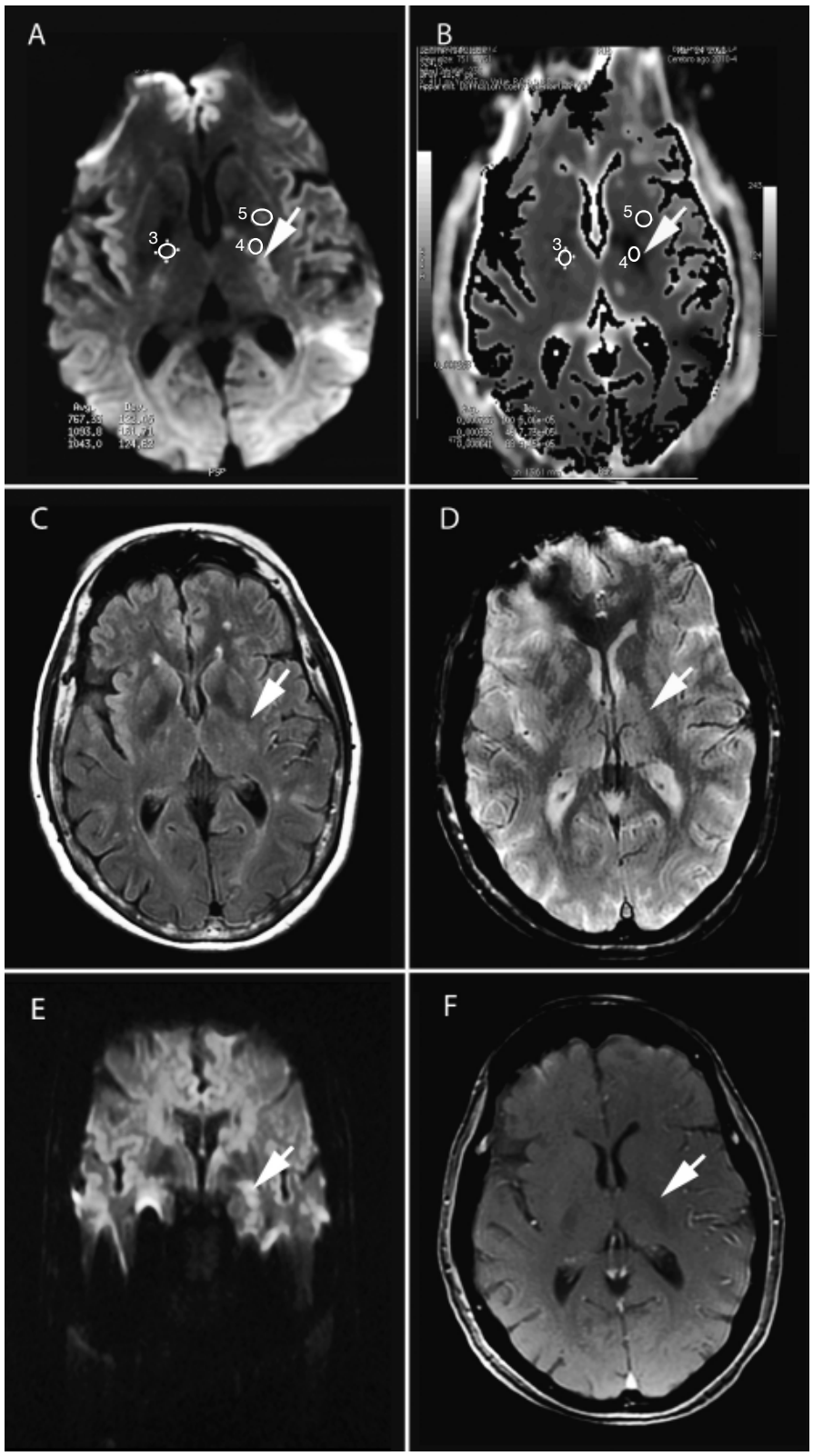

Figure 1. A, B, E. Diffusion-weighted sequence and quantitative post-processing of ADC show hyperintense focal images on left thalamus (white arrows), with ADC decrease. These lesions were not observed on conventional FLAIR (**C**), Gradient Echo (**D**), and contrast-enhanced T1W sequences (**F**) (white arrows).

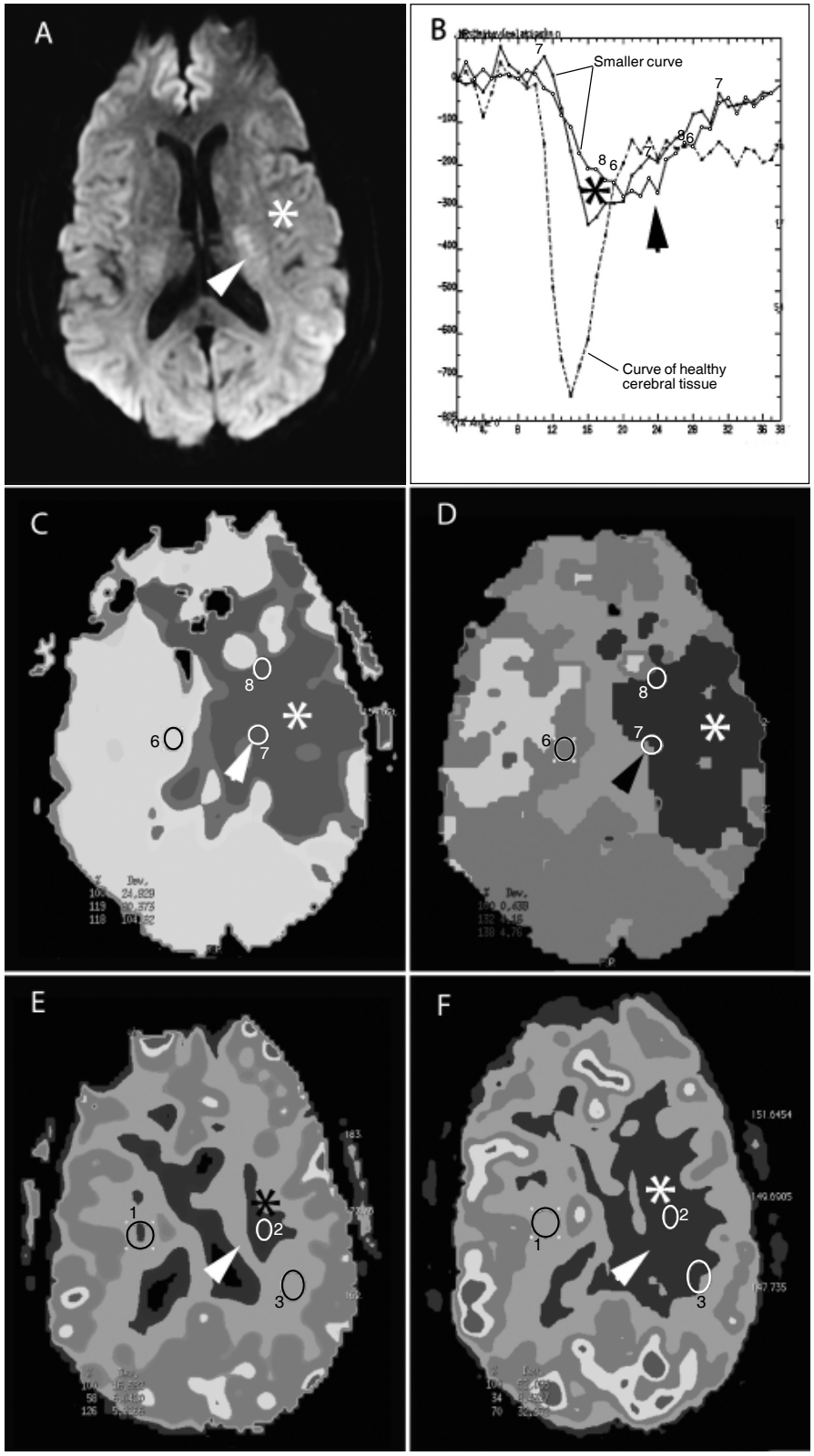

Figure 2. A. Depiction of area of penumbra around the infarcted area on diffusion-weighted sequence. **B.** Typical penumbra perfusion chart: smaller curve (continuous line) with deviation to the right (arrowhead), compared with a typical perfusion curve of healthy cerebral tissue (discontinuous line). **C, E, F.** Semi-quantitative measurement of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT), with increased values of 202, 148 and 103%, respectively. **D.** Time-to-peak (TTP) with a major delay of 10-13 s.

Figure 3. Sequence for the assessment of intracranial vessels (3DTOF). **A, B.** Interruption of blood flow from segment M1 (white arrows) of left middle cerebral artery (MCA). **C, D.** Permeability of both posterior cerebral arteries; right artery shows reduced yet permeable caliber (white arrows).

in addition, the right posterior cerebral artery (PCA) presented a reduced yet permeable caliber (Figure 3A-3D).

DISCUSSION

Unlike muscular tissue, cerebral tissue is very sensitive to ischemia, due to the absence of neuronal energy reserves.[4] In the total absence of blood flow, the available energy stores can maintain neuronal viability for approximately 2-3 min. However, in acute ictus, ischemia is more frequently incomplete, as the injured area of the brain receives some collateral blood supply from uninjured arterial and leptomeningeal areas. Therefore, acute cerebral ischemia can result in a central irreversibly infarcted tissue core surrounded by a peripheral region of shocked cells that constitute the penumbra.[4]

Physiopathology associated to ischemic stroke

In the peripheral areas around an infarcted tissue, evoked potentials are abnormal and the cells cease to function; however, these regions are potentially salvageable by means of early recanalization. At a cellular level, there is an initial cessation of neuronal protein synthesis, followed by a loss of membrane transport and synaptic activity. Further reduction in perfusion pressure eventually causes irreversible stroke. The transition of ischemia from reversible to irreversible depends on the severity of the stroke and the duration of the blood flow decrease. Other factors that play an influential role in this transition include selective vulnerability of specific neuronal groups and the physiological conditions during recanalization.[4] The penumbra is a dynamic process that exists within a narrow range of perfusion pressures; the duration of the delay in recanalization is inversely proportional to the size of the penumbra.[4,6]

The current advancement in knowledge about cerebral physiopathology allows clinicians to read, in the MR imaging report, the information that corresponds to the four points proposed by Rowley.[3] It is important to know that the report of a MR imaging study that comes with a diffusion-perfusion analysis is a legal medical document that can justify to the clinician the application of recanalization procedures the cost of which can exceed 5,000 USD in a private hospital facility.[1] In an infarcted brain, it is possible to identify "four compartments" that are related to the physiopathologic mechanism of the ischemic penumbra. Such compartments can be distinguished on the different MR imaging sequences:

- Normal tissue.
- Hypoperfused tissue (i.e., oligemic tissue, which is generally not at risk).
- Tissues at risk (ischemic penumbra).
- Irreversibly damaged tissue (ischemic core).

Over the last thirty years different experimental studies have revealed the approximate parameters of regional cerebral blood flow (CBF).[1,4] The regional cerebral blood flow of normal tissue is approximately 50-60 mL/100 g/min. The first response of cerebral tissue to the decrease of cerebral perfusion pressure (CPP) is dilating the vessels in the involved territory. The regional cerebral blood volume (CBV) will increase through vascular spaces to maintain the CBF. This mechanism is termed autoregulation and represents the hemodynamic reserve

of the tissue. Such auto-regulatory function will remain intact if the decrease of cerebral perfusion pressure is within a 60-130 mmHg range, which is within the mean arterial pressure range.[7]

The tissue can maintain its cellular integrity in spite of being undergoing a deep metabolic alteration. It can live on in this state until the CBF decreases to less than 10-12 mL/100 g/min (20% below the normal level, the stroke threshold). Such level of oligohemia can be found up to 30-48 h after the symptom onset.[8]

Identification of the penumbra by MR imaging

The area of penumbra can be assessed on MR images (in which the penumbra is indicated by the mismatch between the diffusion and perfusion parameters). The presence of a penumbra has important implications for the selection of an adequate therapy and for the prediction of the clinical outcome.[5] The assessment of a brain by MR imaging implies the acquisition of images in different types of sequences, where each sequence allows a more specific evaluation of some tissues than others (table 2 shows the MR images that currently compose the study protocol of ischemic cerebrovascular disease at the MRI Unit of our medical facility).

The concept of therapeutic window

Since 1995[9,10] the concept of therapeutic window has been established, which refers to the early treatment of hyperacute cerebral ischemia within 0-3 h for intravenous therapy and 4-6 h for intra-arterial thrombolytic therapy.[11,12] Several studies have shown that thrombolysis may be a safe and effective procedure within up to six[13] or 9 h.[6,14] However, the results of more recent studies have shown that intravenous thrombolytic therapy can benefit patients who have been carefully selected based upon the results of diffusion, perfusion, or penumbra on MR images.[15,16]

Advantages of MR imaging over CT

Computed tomography (CT) is a widely available imaging technique for the quick and safe performance of studies; it is relatively available at first and second-rate hospitals. Although the American Heart Association (AHA) recommends in its practical guidelines an initial CT for the exploration of acute cerebrovascular disease (CVD), stroke results are only visualized 3 to 6 h after ictus, and unfortunately up to 60% of CT scans show normal results during the first hours following an ischemic lesion.[17,18] The lesser sensibility and specificity of CT in the diagnosis of an ischemic event restricts the attainable benefits. In this manner, it is only the MR imaging sequences, including the diffusion-perfusion analysis, which can provide thorough information for the diagnosis of acute stroke, with a sensibility greater than 80% (as shown in the assessments of the MR studies performed within the first hours following the ischemic event), compared with the 60% sensibility of CT that is normally used for reports.[19,20]

MR imaging sequences used for the assessment of CVD

The complete assessment of acute stroke can be performed by means of a combination of conventional MR

Table 2. Protocol sequences for ischemic CVD that allow an imaging depiction of affected tissues by stroke.

Sequences	Evaluated tissue	Observations.
Diffusion-weighted	Infarcted tissue (cytotoxic edema)	Findings observed in 30 min.
Perfusion (penumbra)	Ischemic tissue	Findings observed in min.; requires gadolinium.
FLAIR	Cellular edema	Findings observed in 4-6 h.
T2W	Vasogenic edema	Findings observed in 12 h.
Gradient echo	Hemorrhagic infarct	Differentiation between ischemic and hemorrhagic infarcts.
3 DTOF	Arterial circulation conforming Willis polygon	Does not require gadolinium.
Carotid angioresonance	Intra and extracranial internal carotid artery	Requires an additional gadolinium dose to the one used in the perfusion sequence; has to be requested as an additional sequence.

imaging, MR angiography, and post-gadolinium diffusion and perfusion-weighted sequences. Conventional MR imaging sequences detect acute cerebral ischemia during the early minutes following the onset of the cerebrovascular accident. As a benefit, conventional MR imaging has the additional advantage of showing the pathologic entity (cerebrovascular accident and its mimics) on different planes. The employed sequences include T1W spin-echo; T2W; FLAIR, and T1W post-gadolinium. Typical findings include hyperintense signal intensity of white matter on T2-weighted and FLAIR images, with a consequent loss of gray matter and of matter differentiation. Such techniques allow the detection, in addition to that of ischemic tissue, of very small coexisting areas of cerebral hemorrhage, which may be present in some patients with acute ictus.[21]

Conventional sequences are less sensitive than diffusion-weighted images during the first hours following the ischemic event (hyperacute stage), and can lead to false-negative results. Starting from the acquisition of diffusion-weighted images, conventional MR imaging sequences play a complementary role. On diffusion-weighted images, ischemic tissue appears as hyperintense (with a white or light gray intensity), compared with normal cerebral tissue.[22,23]

Diffusion quantification is known as apparent diffusion coefficient (ADC); it shows a decrease of speed diffusion of the protons in the hydrogen atoms of the cerebral tissue molecules, within the first 30 minutes following the ischemic onset.[24,25] ADC continues to further decrease and reaches its lowest point in approximately three to five days. From there, the product starts increasing again and returns to the reference value approximately one to four weeks afterwards. This is probably due to the development of vasogenic edema, along with the persistence of cytotoxic edema.[24,25]

Diffusion-weighted imaging (DWI) delineates regions of bio-energetic compromise, where sodium-potassium ATPase activity has failed. Protons that are not moving (restricted diffusion/cytotoxic edema) are associated with higher signal on DWI, and the apparent diffusion coefficient (ADC) is its quantitative measure. In areas of deeper energetic compromise and sequestration of water molecules, ADC values are lower.[11]

Perfusion-weighted images (PWI) are acquired by using the dynamic-susceptibility contrast imaging technique. A series of susceptibility-weighted images (i.e., T2-weighted images) are obtained every 1-2 s during an injection of intravenous contrast material (gadolinium). As contrast transits the cerebral circulation, the MR T2* signal intensity of the images successively decreases due to the paramagnetic nature of the contrast, and then returns to normal. This change in signal intensity is plotted as a function of time (the signal-intensity time curve). The central volume principle is used to calculate the relative cerebral blood flow (rCBF) and relative cerebral blood volume (rCBV) on a voxel-wise basis; rCBF is proportional to the amplitude of the signal intensity time curve, while rCBV is estimated from the area under the signal-intensity time curve.[26] PWI allows the visualization of areas of altered blood flow.[27] Areas of hypoperfusion can also be visualized as bolus arrival time or tissue with delayed time-to-peak (TTP), the first moment of the curve corresponding to the apparent mean transit time (MTT). Voxel-wise values for each parameter are assigned a color code or intensity value, and then maps are constructed to for rCBF, rCBV, TTP and MTT.[26,28]

Table 3. Typical findings of diffusion-perfusion analysis.

Finding	Meaning	MTT/TTP	CBV/CBF
1. Smaller infarcted area on diffusion than the ischemic area size on perfusion.	Typical finding of ischemic stroke with the presence of penumbra.	Increased	Decreased at early stages
2. Infarct and ischemic area of the same size.	Ischemic stroke without penumbra.	Normal	Both increased
3. Larger infarcted area on diffusion than the ischemic area size on perfusion.	Can signify that a patient received thrombolytic treatment and that the penumbra continues progressing in spite of the infarct.	Normal or decreased	Both increased
4. Normal diffusion with the presence of penumbra on perfusion.	Ischemia that conditions neurological symptoms (that prompt the clinician to request a MR study to confirm the perfusion alteration); the tissue is at risk (penumbra) but not infarcted.	Increased	Decreased CBF

Table 4. Acquisition Times for CVD Protocol at 1.5 and 3.0 T (MRI Duration at our Medical Facility).

CVD Protocol at our Magnetic Resonance Imaging Unit	Imaging Acquisition Time per Equipment	
	1.5 Tesla	**3.0 Tesla**
FLAIR	4 min	3.72 min
T2W	2 min	2 min
Contrast-enhanced T1W	30 s	21 s
Gradient Echo	2.52 min	1.28 min
3 DTOF	3.56 min	3 min
Diffusion-weighted	1.19 min	54 s
Perfusion-weighted	1.09 min	1.08 min
TOTAL	**14.66 min**	**11.83 min**

In a few weeks the affected area develops gliosis, with a subsequent increase in the amount of extracellular water.[24,29] Amongst the different types of perfusion maps, TTP and MTT show the ischemic areas, although sometimes they may reflect an overestimation of the final size of the infarct, while CBV maps tend to underestimate the final magnitude of the infarct. On occasions, there is no correlation between the diffusion and CBF maps, which represents important findings for the clinician in predicting the stroke evolution. CBV maps have been more closely related to changes in the size of the infarct at follow-up.[5] Table 3 shows the diffusion-perfusion analysis.

Clinical application

A medical facility with an adequate structure for the evaluation of acute stroke is one that has a MR imaging unit that works 24/7, all year round (holidays included), where a cerebrovascular disease protocol has already been set up for the radiologists to follow and perform. It is important for the clinician to know that it is possible to evaluate carotid arteries on angioresonance sequences at the same time of perfusion assessment-hence its inclusion in the evaluation needs to be requested. Table 4 shows that the time it takes to perform a protocol for CVD does not exceed 15 min of machine use; the application of such protocol is therefore thoroughly justified, because it allows, in such a short period, to identify whether an area of penumbra exists, as well as determining all hemodynamic values. All of this, along with the available clinical data, will help decide what treatment choice is the most adequate in each case.

CONCLUSIONS

It is essential to have a deep knowledge of ischemic penumbra, not only for the understanding of the ischemic process itself, but also for the generation of a fundamental framework for therapeutic decision-making.

One of the main reasons why acute stroke is such an interesting field for radiologists is the advancement in application of MR techniques, such as diffusion and perfusion-weighted images of the brain, which have led clinicians to a better understanding of the physiopathologic mechanisms of cerebral ischemia and stroke.

Diffusion and perfusion-weighted images are complementary imaging methods that allow the identification of an ischemic event as early as 30 min after its onset; this advantage, along with the simplicity and readiness by which a CT or MR angiography is performed, has led to the setup of stroke working teams, both worldwide and in Mexico, for the vascular rescue of patients with ischemic disease.

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