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A calculation method for semi automatic follow up of multiple sclerosis by Magnetic Resonance Eco Planar Perfusion Imaging

Giuseppe Placidi[a], Mylene Sabatini[b], Massimo Gallucci[b], and Antonello Sotgiu[a]

[a]*INFM, c/o Centre of Magnetic Resonance, University of L'Aquila, ITALY*

[b]*Department of Radiology, University of L'Aquila, ITALY*

Abstract

Multiple sclerosis (MS) is one of the most common chronic and disabling inflammatory and demyelinating disorders of the central nervous system (CNS). Magnetic Resonance Imaging (MRI) allows the observation of pathological changes in vivo. It has provided a number of important insights into the spatial-temporal evolution of MS pathology in vivo. Conventional MRI with T2-weighted images is useful in the assessment of oedema early in the inflammatory stage, tissue destruction with demyelination and axonal loss, and gliosis later in the chronic stage. Examination by conventional MRI usually requires more than one hour and it does not completely reveal rapid dynamic changes in blood flow. Recently introduced rapid MRI techniques, MR perfusion imaging and MR diffusion imaging, allow measurement of pathophysiological changes at the cellular level with a good temporal resolution. Nevertheless, until now there were no adequate analytical methods available within the clinical routine to differentiate between types of MS lesions using fast perfusion MRI. We present an analytical method capable of recognizing, and distinguishing, the status of MS lesions by calculating some numerical parameters from the MR perfusion images. The method has been tested on 14 patients affected by MS with different lesions and the results have been compared with those obtained with more expensive conventional MRI examinations. The proposed method made it possible to recognize the nature of the MS lesions in 100% of the examined cases without the need to perform long conventional MRI examinations, using instead perfusion MRI eco planar imaging which takes no more than two minutes. Moreover, the reduced time also allowed reduction of the quantity of contrast medium administered to the patient. Further studies may lead to the use of this technique for differential diagnoses in other white matter diseases.

Keywords:

Multiple Sclerosis, MRI, Perfusion Imaging, EPI.

1. Introduction

Multiple sclerosis (MS) is one of the most common chronic and disabling inflammatory and demyelinating disorders of the central nervous system (CNS). It affects about 0.1% of the population in temperate climates. In 80-90% of cases, MS starts with a relapsing-remitting course (RR-MS). The remaining 10-20% of patients begin the disease course by experiencing gradually progressive neurological deficits (primary progressive disease, PP-MS) without acute relapses. However, approximately two-thirds of patients with RR-MS eventually undergo a similar fate (secondary progressive phase, SP-MS) as relapse frequency decreases over time [1].

In vivo Magnetic Resonance Imaging (MRI) allows the observation of pathological changes and it has also provided a number of important insights into the spatial-temporal

evolution of MS pathology [2-3]. First of all, imaging studies have revealed differences between RR-MS and PP-MS. In patients suffering from RR-MS, acute lesions with spontaneous resolution are frequently detected in areas of white matter, even in the absence of clinical attacks. These lesions are often characterized by a disturbance of the blood-brain barrier (BBB), local oedema and demyelination which are typical features in an inflammatory process. By contrast, when progressing to the secondary phase and in patients with PP-MS such inflammatory activity is lower, while global brain atrophy becomes more evident and seems to correlate with disability.

Conventional MRI with T2-weighted images is useful in the assessment of oedema early in the inflammatory stage, tissue destruction with demyelination and axonal loss, and gliosis later in the chronic stage. T1-weighted lesions are suggestive of acute oedema or tissue destruction (chronic "black holes"). The use of gadolinium as intravenous contrast medium may reveal any increase in BBB permeability due to inflammation, enabling the differential diagnosis between recent and more temporally remote plaques. Therefore, in addition to its value as a diagnostic tool, MRI has become a surrogate marker to monitor disease progression and response to therapy.

The disadvantage of using conventional MRI is that a conventional examination usually requires more than one hour and it does not completely reveal rapid dynamic changes in blood flow. Recently introduced rapid MRI techniques, MR perfusion imaging and MR diffusion imaging [4] show that pathophysiological changes at the cellular level can now be revealed as early as the initial diagnostic examination. Nevertheless, although Brain Perfusion imaging has been methodologically assessed [4], until now there were no adequate analytical methods available within the clinical routine to assess the differences between different types of MS lesions so as to use Perfusion MRI as a diagnostic and a follow-up tool.

In what follows, we present an analytical method capable of recognizing, and distinguishing, the status of MS lesions by calculating some numerical parameters from the MR perfusion images. The method has been suggested by the pathophysiological differences between MS lesions in different phases: acute lesions are characterized by the presence of inflammation, i.e. augmented blood flow; chronic lesions are characterized by tissue atrophy, i.e. reduced blood flow. In order to underline these differences with a calculation method, we first introduce the MR perfusion signal and the parameters which contribute to these differences, then we describe the method, and finally we present preliminary results of the application of the method to 14 patients affected by MS with different lesions and compare the results with those obtained with more expensive conventional MRI examinations.

2. Materials and Methods

2.1. Perfusion MRI

Functional magnetic resonance imaging, with the diffusion and perfusion imaging techniques, now offers new possibilities for diagnosis and follow-up of MS lesions by monitoring some hemodynamic parameters over time. MRI now provides access to information on cerebral perfusion that is of importance for the diagnosis and therapeutic follow-up of various brain pathologies [4-5]. To understand the influence of blood on the MR signal is a key issue in deriving accurate information about perfusion, either in healthy or in pathological conditions. Perfusion imaging reveals disturbances in the microcirculation to be the underlying cause of the changes in the parenchyma. In addition, imaging of the relative cerebral volume and the bolus transit times demonstrate the initial compensation mechanisms of the vascular system. It is possible to obtain useful information by comparing the values of the temporal parameters of the perfusion signals of

different image districts. A further goal of MRI perfusion studies is the assessment of regional perfusion from MR image intensity. An MR approach to detect and characterize the microvascular circulation is based on the injection of an intravascular contrast agent, such as gadolinium chelates. In MR perfusion imaging, the passage of a bolus of contrast agent through the brain parenchyma is imaged by dynamic T2*-weighted MRI. Information on the regional microcirculation is derived from changes in the resulting MR signal.
There are many different methods of monitoring the bolus passage through the blood circulation system [6], but the reference method is eco-planar imaging (EPI) [7]. Thanks to this rapid imaging technique, it is possible to irradiate a set of 10 sample slices in about 80 seconds; each slice is collected 40 times, with 2 seconds time separation between consecutive images.
A T2*-weighted imaging sequence is used to collect in each voxel the signal-vs-time curve. The signal intensity is converted to a relative measure of the contrast agent concentration by the following relationship:

$$c(t) = -\frac{k}{T_E}\ln\left(\frac{s(t)}{s(0)}\right) \qquad (1)$$

where T_E is the echo time and k is an unknown proportionality constant.

The bolus passage can be determined for every volume element (voxel). The signal/time curve (corresponding to the concentration/time curve) can be used to determine important hemodynamic parameters: cerebral blood volume (CBV); cerebral blood flow (CBF); mean transit time (MTT); time of bolus arrival (TA); time of peak (TP); width, measured at half height, of the curve peak describing the signal loss over time (FWHM).

2.2. The Calculation Method

The calculation is performed by taking into account the differences between the MS lesions, i.e. the fact that acute lesions show mainly an inflammation and chronic lesions are dominated by tissue atrophy and destruction (reduced blood flow). In fact, by considering these two particular differences, we aimed to find differences in the perfusion signal inside the lesion with respect to those in the contralateral region. As previously discussed, the injection of a paramagnetic contrast agent into the blood circulation has the effect of reducing T2 both inside the blood circulation and inside the cerebral region situated in proximity to veins and arteries. These effects are more or less irreversible due to the time the paramagnetic substance remains inside the region of interest (ROI). In the presence of a chronic lesion, the paramagnetic agent arrives later than in normal tissue and the perfusion signal will have TA greater than that registered from the perfusion signal of normal tissue. Moreover, after its arrival, the bolus of the contrast agent will remain longer inside a lesion than in normal tissue: the effect is to enlarge the peak of the lesion signal with respect to the contralateral apparently healthy signal (stagnation effect). This fact can also be explained as an irreversible loss of phase coherence inside the region containing the lesion. Conversely, an acute lesion, showing mainly an inflammatory nature, will have a faster recovery of the T2 reduction effects with respect to the contralateral apparently healthy tissue, due to the augmented blood flow. Also, the magnetic susceptibility effects are reduced and reversible. A direct method of characterizing each lesion results from the use of these differences in the perfusion signals of MS lesions with respect to their own contralateral apparently healthy tissue. Indicating with ? $TA=TA_L - TA_N$, where TA_L and TA_N are the TA values calculated from the perfusion signals inside lesion and apparently healthy contralateral tissue respectively, and with ? $FWHM=FWHM_L - FWHM_N$, where $FWHM_L$ and $FWHM_N$

are the FWHM values calculated from perfusion signals inside the lesion and apparently healthy contralateral tissue, the following method was adopted:

1) Calculate the perfusion signal inside the lesion;
2) Calculate the perfusion signal in a contralateral apparently healthy tissue region;
3) Normalize the signals;
4) Calculate ? TA and ? FWHM on the normalized signals;
5) If ? TA and ? FWHM both have a positive value, the lesion can be considered NON ACTIVE (chronic), else,
   If the ? TA and ? FWHM have opposite signs, the method is unable to define the lesion status, else the lesion is considered ACTIVE (acute).

The comparison of damaged tissue with apparently healthy contralateral tissue is due to the need to eliminate from the bolus arrival the retard effects due to physiological objective parameters, such as cardiac cycle or blood pressure, which makes it impossible to establish the peak retard (or anticipation) and enlargement (or restriction) strictly due to the lesion status. The situation in which ? TA and ? FWHM have opposite signs is impossible because it would indicate opposite lesion conditions: both ACTIVITY and NON ACTIVITY. However, data noise and experimental errors can also allow the verification of such a situation.

3. Results

Fourteen patients suffering from definite MS underwent MRI examination on a 1.5 T unit (GE, Signa Horizon). After conventional T1-w and T2-w sequences, a series of SE echo planar images (TR 2000 msec; TE 80 msec; slice thickness 5.5 mm; slice interval 2 mm; matrix 128x128; nex 1) covering the cerebral hemispheres was acquired 40 times during 1 min and 21 sec. Meanwhile, a Gd-chelate at the standard dose of 0.1 mMol/ Kg b.w., followed by 15 ml of a saline solution, was administered through an 18 gauge needle placed into the ante-cubital vein using an automatic injector. In the post-processing, the signal intensity-versus-time curves were obtained, according to Eq.1, and the relative time of contrast medium arrival, TA, and function width, FWHM, were calculated for ROIs placed into both the lesion and the normal-appearing white matter of the opposite hemisphere at the corresponding site. Differences between the values registered in damaged and normal-appearing white matter were calculated for both TA (? TA) and FWHM (? FWHM) and were compared to enhanced T1-w images in order to define their ability in depicting lesion activity.

Twenty-six T2-w hyper-intense plaques were assessed; among these 10 had shown a BBB breakdown on Gd enhanced T1-w images and were considered as active lesions. Thirty-six ROIs placed within the plaques were analysed. For some larger lesions, we considered multiple ROIs due to the lesion heterogeneous aspect on Gd-enhanced T1-w scans. The numeric data obtained were normalized and analyzed blindly by a Computer Scientist using the previously described method. The quantitative analysis of our findings is reported in table 1.

Table 1

Number of ROIs	□TA sign	□FWHM sign	Perfusion MRI and Calculation Method	Conventional MRI
5	=0	=0	Active	5 Enhancing (Active)
24	=0	=0	Non Active	24 Non enhancing (Non Active)
3	0	=0	Active	3 Enhancing (Active)
4	=0	0	Active	4 Enhancing (Active)

Our data show that the negative value of at least one of the two different parameters corresponds to an enhancing ROI, while the positive value of at least one of them or the null value of both will correspond to a non-enhancing ROI. We found 12 ROIs with perfusion findings suggestive of BBB breakdown, confirmed by enhancement at standard imaging. 24 ROIs showed patterns of normal BBB function and no enhancement was evident at the corresponding sites. As shown in the table, there were no cases in which the above-mentioned parameters exhibited opposite signs: this is in accordance with what has been previously stated.

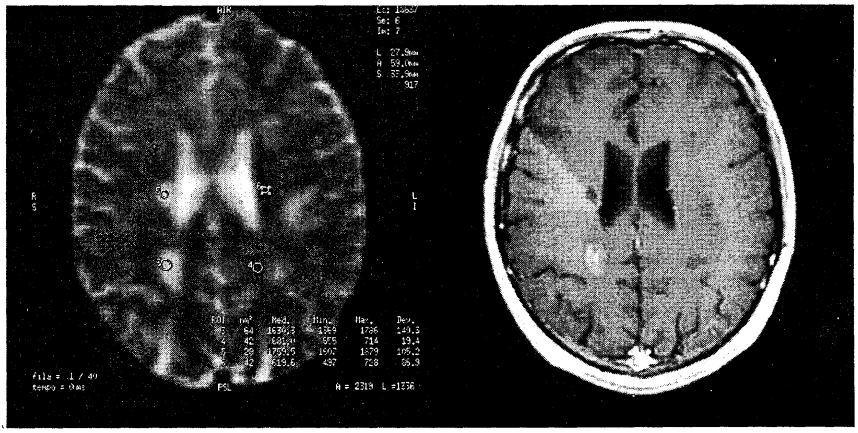

Figure 1. MR EPI (left) and T1-w SE (right): the lesions are highlighted by indicated ROIs. ROI 3 is placed on an great active lesion, ROI 5 is placed on a non active lesion, as highlighted by the enhancement in the right image. ROIs 4 and 6 are placed on the contralateral zones of ROIs 3 and 5 respectively.

As an example, figure 1 reports both the first Perfusion EPI image (left), of a sequence of 40, and the T1-w image (right) of one examined patient affected both by acute and chronic lesions. ROIs have been taken inside the lesions and inside contralateral zones and the normalized signals versus time are depicted in figure 2. The analysis of the signals reveals the values of ? TA and ? FWHM are both negative for the acute lesion and positive for the chronic lesion. These information have been calculated by using signals collected by the sequence of 40 Perfusion EPI images and the T1-w images have been collected just for confirmation.

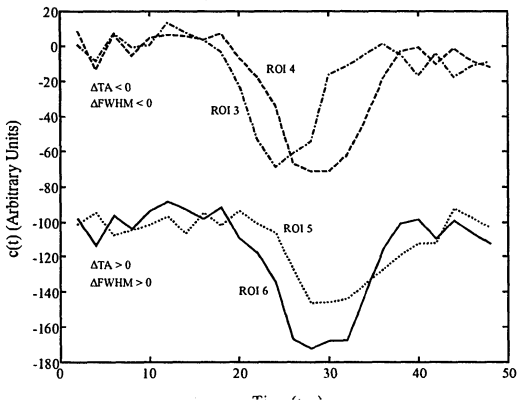

Figure 2. The contrast agent concentration signal versus time is indicated for each of the ROIs indicated in figure 1. The signals referred to the ROIs 5 and 6 have been offset to separate information referring to different lesions. ROI 4 and ROI 6 represent the signals corresponding to contralateral zones of each lesion.

4. Conclusions

The present study demonstrates that this method is highly sensitive (100%) (36 out of 36 cases) in depicting BBB breakdown in MS cases, defining typical patterns of normality and damage. The proposed method makes it possible to recognize the nature of MS lesions without the need to perform long conventional MRI examinations, by using perfusion MRI eco planar imaging which takes no more than two minutes. Moreover, it allows the use of an automatic method to calculate the status of a lesion, having previously defined a region of interest. Moreover, the reduced time also allows a reduction in the quantity of contrast medium administered to the patient. Further studies are needed to better define the specificity of our results, mostly in order to propose this technique for differential diagnoses in doubtful cases of white matter diseases.

5. References

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6. Address for correspondence

Giuseppe Placidi, Ph.D. INFM, c/o Centro di Risonanza Magnetica, Università de L'Aquila, Via Vetoio Coppito II, 67010 Coppito, L'Aquila, ITALY.
E-mail addresses: Placidi@fismedw2.univaq.it
Giuseppe.Placidi@cc.univaq.it