ROLE OF DIFFUSION-WEIGHTED IMAGING (DWI) IN MAGNETIC RESONANCE (MR) OF THE BREAST

F.Odoguardi, A.Cilotti, C.Marini, M.Moretti, D.Mazzotta, A.Vaccaro, C.Iacconi, F.A.Cardillo, A.Starita.

University of Pisa, Italy

ABSTRACT

DWI-MR provides new and different information about the biophysical proprieties of tissue. The use of powerful, precise and actively shielded gradients permits to perform Echo-Planar Imaging (EPI) and acquire an images in a very short time (below 200ms) (1). The consequent reduction of macroscopic motion effect makes possible the use of DWI in detection and characterization of abdominal lesion (liver, pancreas, adrenals) and in breast MRI imaging. Dynamic contrast-enhancement provides information related to vascularity of breast lesion but no information about its cellularity, which is another important index of tumor grade. In DW imaging two short-duration gradients of opposite polarities are applied for sentitising MR to detecting early changes in morphology and physiology of tissue associated with the state of molecular translational motion of water and its changes, such as in the permeability of cell membranes changes, cell swelling, cell lysis. The decreased Apparent Diffusion Coefficient (ADC) in breast cancer reflects the underlying histological pattern of densely packed randomely organized tumor cells, which inhibit effective motion of water molecules and restrict diffusion. DW MRI can anticipate diagnosis showing early molecular changes and helps in breast lesion differential diagnosis. A potential application is in monitoring early response to treatment (2).

Keywords: magnetic resonance imaging, diffusion, breast cancer

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INTRODUCTION

The request for more frequent physical and strumental examinations implies earlier diagnosis and improved prognosis. Breast MRI is currently used to accurately diagnose primary and recurrent breast cancers, particularly when mammography and breast US are inconclusive or yield discrepancies. MRI may also improve local staging by detecting multifocal tumor in patients candidate for conservative breast surgery. While the excellent sensitivity of breast MRI has been demonstrated, its low specificity continues to represent a limit, particularly in patients referred for further clarification of an inconclusive conventional breast imaging finding. In an effort to increase MRI specificity, it's important to improve morphological and pharmacokinetic data acquisition and find a compromise pertaining to both spatial and temporal resolution (5). In addition DWI represents another resource that in some cases, combined with morphology and enhancement pattern, can help in differentiating breast lesions.

PHYSICAL ASPECTS OF DIFFUSION

The diffusion of water molecules correlates with the structural characteristics of tissues in physiological and pathological conditions (1). Diffusion describes the microscopically visualized thermally induced behaviour of molecules moving in a random pattern; this phenomenon is quantified by means of an apparent diffusion coefficient (ADC) that depends, in tissues, on the presence of barriers to the water diffusion, such as macromolecules and membranes (2)

In a tissue, water molecules are subject to two types of motion: "orderly " (e.g. the motion of blood within a vessel) and "random" (related to the thermal energy). This random motion, also known as Brownian motion, lies at the basis of diffusion phenomena. Fick 's laws describe the behaviour of a solute which moves along a concentration gradient: in this case the diffusion coefficient is a macroscopic quantity which characterises the phenomenon and which reflects the constant of proportionality which links the flow of particles to the concentration gradient. In homogeneous fluids, macroscopic flow is no longer observed and reference needs to be made to a probabilistic model to describe the motion of the molecules. The probability function which describes motion in an isotropic solution has Gaussian distribution. The diffusion coefficient characterises the motility of the molecules of a given fluid and depends on the temperature of the sample.

The diffusion coefficient describes the distance covered by a molecule in its stochastic motion in a unit of time, and is measured in length x length / time (expressed in $mm^2\ s^{-1}$). Therefore a particle with high diffusion will cover an extensive area, whereas a particle with low diffusion will cover a limited area (1).

MRI AND DIFFUSION OF WATER MOLECULES

The study of water molecules diffusion in tissues provides useful informations about the microscopic

structure of the tissues themselves and the processes taking place within them. In the presence of a magnetic field gradient, the spins accumulate different phase shifts (which produce a loss in the MR signal) caused by their diffusion motion. In practice, this effect is tiny and it is necessary to sensitising the MR sequences to diffusion so as to render the phenomenon of diffusion measurable: the solution is the application of short-duration gradients of opposite polarities, of equal intensity and duration separated by a time interval. The accumulated phase by spins depends on their movements occurring in the time interval between the application of the first and second gradient. The phase will be 0 if the spins are stationary, variation of phase is observed if they are moving orderly at the same velocity; if movement is random, different spins acquire different phase variations, thus resulting in a loss of signal, described by:

$$\mathbf{S = S_0 e^{-bD}}$$

where S and S_0 are respectively the signal intensities with and without diffusion sensitisation, D is the diffusion coefficient and “b” expresses the level of sensitisation to diffusion of the sequence (fig. 1).

In a homogenous and isotropic medium in which the motion is independent on direction, by using different diffusion-weighted images (at least two) obtained for different b values, it’s possible to calculate the diffusion coefficient map (1). Low diffusion corresponds to lower signal loss, whereas high diffusion corresponds to a higher signal loss (e.g. the liquid contained in a cyst).

SEQUENCES

As anticipated, diffusion can be studied using an appropriately structured sequence with a supplementary dephasing gradient: in this way the spins accumulate a phase change dependent on their position with respect to the gradient. A second gradient equal and opposite to the first is then imposed which induces a complete rephasing in the stationary spins and an incomplete rephasing in the mobile spins. As a consequence the mobile spins induce a signal loss proportional to their motion. As regards the signal, the greater their displacement the greater is the loss of signal with respect to that produced by the same stationary spins. Strong sensitisation gradients are required. To this end most manufacturers produce MR devices with sufficiently powerful gradients (at least 20 m T/m). In order to obtain good-quality diffusion-weighted MR Images, powerful gradients are required with high intensity and fast rise times (high b with short time intervals) which are precise (identical successive gradients) and without contaminated magnetic fields (short gradient coils, active shielding of the gradients).

As regards sequences, conventional Spin Echo (SE) sequences have the greater disadvantage of lasting several minutes, and when they are used to acquire diffusion weighted images they require that the patient remains totally immobile. Clearly, if the signal loss in diffusion-weighted images is produced by the Brownian motion of the water molecules, macroscopic motion, such as heart beat and respiration, conceals the microscopic variations of the diffusivity of the various tissue components. Macroscopic motion is therefore exceedingly deleterious to the signal of diffusion-weighted images, to the point of almost completely cancelling out the signal itself. The use of increasingly powerful and actively shielded gradients has enabled the passage from SE sequences to echo-planar imaging (EPI) sequences. This technique is capable of acquiring "instantaneous" images with a temporal resolution below 200 ms, which minimizes the deleterious effect of macroscopic motion. In practice, EPI acquires all the echoes used to obtain an image after a single excitation pulse (single-shot technique) or after each excitation many but not all echoes are acquired (multishot technique). The latter is a technique where the reading occurs with a gradient echo, in that the frequency encoding gradient is rapidly oscillated to obtain the

different echoes. The technique is highly dependent on the quality of the gradients both in terms of intensity and particularly in terms of the rise time (1). Although image distortion due to the susceptibility associated with single-shot EPI tends to increase with a larger b value, DWI without breath holding is acceptable when the maximum b value of 1000 is used. Diffusion weighted MR images are acquired using a multisection SE type single shot EPI sequence in the sagittal plane. Sensitizing diffusion gradient are applied sequentially in the x-. y-, and z directions with different b. In order to locate the solid portion of the lesion accurately, Gd-enhanced Fast Gradient Echo 3D are performed (5).

DATA ANALYSIS

DWI provides essential qualitative information regarding the degree of diffusivity of the water molecules in a given tissue (high or low diffusivity). However, the DW images have an intrinsic component of T1 weighting, DP and above all T2 weighting, in variable proportion depending on the value of TE used. The so-called "T2 shine-through" phenomenon is a typical example of T2 signal which plagues the DW image. Owing to this phenomenon a DW image with a signal which should be low (e.g. free water in the tissue), would instead appear with a high signal, due to a lengthening of the T2 linked to the water contents (1).

The acquisition of at least two images with different degrees of diffusion weighting, that is with different b values (e.g. 0 and 1000 s/mm^2), allows to calculate ADC maps and mean diffusivity. Software calculates automatically the ADC and its value is more precise if many diffusion-weighted images are used (Fig. 2).

These are no longer qualitative images, but rather quantitative maps, in which the signal intensity of each voxel represents the mean diffusivity (along the direction selected by the gradient) in the voxel itself. Tracing regions of interest (ROI) on these maps enables the measurement of the ADC along various axes, in different tissues and the comparison of possible variations over time of pathological processes (1). ROI is minimally smaller than the actual solid portion of the breast lesion and it's carefully placed to ensure that adjacent areas are not included (5).

We must add that in biological tissues microscopic motion includes molecular diffusion of water and blood microcirculation in the capillary network. Both diffusion and perfusion therefore affect the ADCs obtained from biological tissues. In breast tumors, although higher microvessel counts are recorded for malignant than for benign pathology they show a lower mean ACDs than the benign lesions do. This suggests that molecular diffusion of water has a greater impact on the ADCs with respect to perfusion in case of breast lesions (5), in particular if sufficiently high b value is used.

USEFULNESS OF DWI

MRI mammography is a tool in the differential analysis of breast lesions. Furthermore, it has also demonstrated that Gadolinium (Gd)-enhanced MRI depicts breast cancer with exquisite sensitivity. In addition, with the exception of occasional cases of isolated ductal carcinoma in situ (DCIS), virtually all pathologically proven breast cancers have been detected in several large trials. The classification of breast lesions obtained by combining three independent classes of features (boundary descriptors, uptake parameters, and texture features) has shown an increased specificity. However, a significant overlap in the enhancement patterns of malignant breast lesions and fibroadenomas still exists (1); sometime fibroadenomas have characteristics that mimics malignant lesions in both ultrasound and dynamic contrast enhanced MRI studies. The latter give us information about changes in vascularity, vascular permeability, interstitial pressure and extracellular

space, but no direct information about tumor cellularity, which is an important index of tumor grade. The proliferative activity of the hyperplastic parenchymal cells of benign breast lesions shows an enhancement pattern similar to cancers and it is not possible to distinguish benign lesion from malignant ones basing on the time-intensity enhancement, because of this confounding overlap. DWI provides information about early changes in morphology and physiology of tissues associated with changes in water content, such as changes in the permeability of cell membranes, cell swelling, and/or cell lysis (2).

Preliminary studies that measured the ADCs in both the normal breast and in breast lesions demonstrated that benign-lesions and normal breast tissue have larger ADCs than those obtained from malignant breast tumors. These findings suggested that cell density might play an important role in the different ADCs obtained from benign and malignant breast lesions and the measurement of extracellular water content may be an additional feature that can improve MRI specificity (1). For example, an increase of intracellular tissue, due either to swelling or to increased cellular density, will cause a decrease in ADC: low values of ADC in malignant tumors reflect the underlying histological pattern of densely packed randomly organized tumor cells, which inhibits effective motion of water molecules and restricts diffusion (fig. 3).

On the other hand, the higher ADC values of cystic or necrotic area reflect a lack of significant restriction of diffusion of water molecules due to the cell loss and consequent expansion of the extracellular space (2).

Some authors demonstrated ADCs would be effective in distinguishing between invasive carcinoma and fibroadenomas. Generally the latter shows lower signal intensity on DWI and this fact can be a limit because lesion <1cm cannot be detected. The same authors point out that duct ectasia and intraductal papilloma are often misclassified: papilloma may have low ADCs in relation to its high cellularity and can be misdiagnosed as malignant; scirrhous carcinoma and Ductal Carcinoma in Situ (DCIS), extremely troublesome to classify based on their morphologic properties and enhancement profiles alone, are still difficult to be correctly classified by DWI. In particular small lesions (<1cm) such as DCIS cannot be visualized on DWI images (5).

As regards agreement between the ADCs of tumor and cellularity as determined from histological analysis, DWI studies on brain tumors have clearly established a direct correlation. The correlation of cell density with ADC has also been established in a study that evaluated ADC as a marker of brain and breast tumor therapeutic response (3).

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Figures:

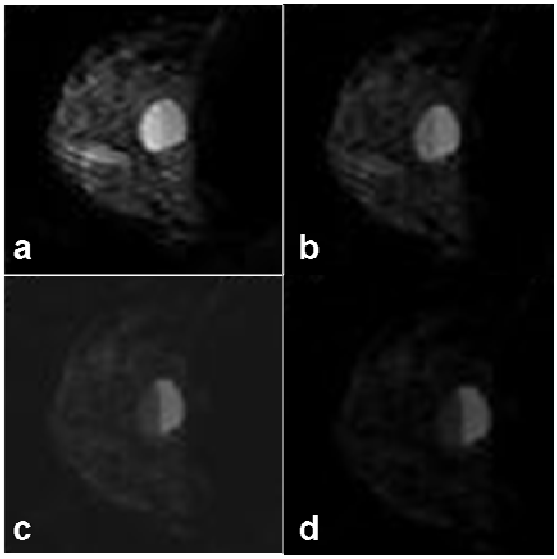

Fig 1. As “weighting " in diffusion increases, so too does the evidence of double intracystic level. Image a, b and c have b value set respectively on 0, 500 and 1000. In the subtraction image (d) fluid-fluid level of the cyst is well shown and mean ADC value is obtained ($2,3x10^{-3}$ mm^2/sec).

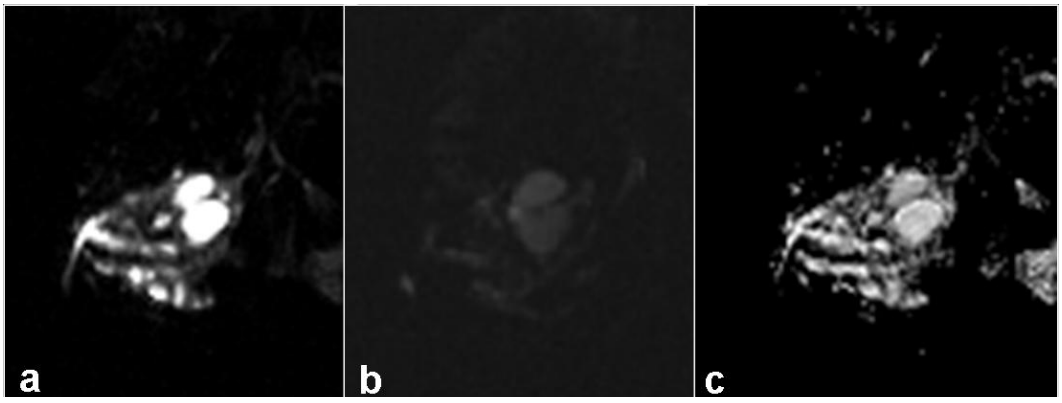

Fig 2. Diffusion weighted images of two cystic lesions: b value is set on 0 (a) and 1000 (b). The subtraction of these images (c) and ADC computation are performed (ADC=2.2x10^{-3} mm^2/sec).

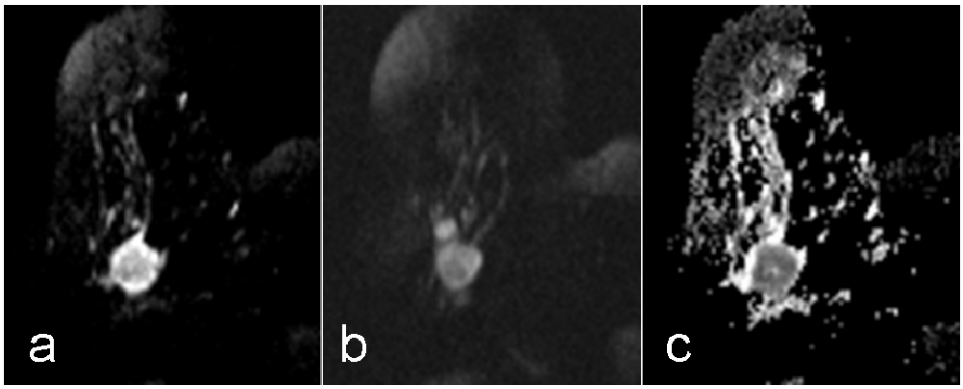

Fig 3. EPI of breast cancer with b=0 (a) and b=1000 (b): subtraction of image (c) and ADC computation suggests a low diffusion of water molecules (ADC=0.87-1.08x$10^{-3}$$mm^2$/sec).