Lesion Characterization Using Vessel Permeability Map to New Blood Pool Contrast Agent Calculated From Dynamic Magnetic Resonance Images

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Use of contrast enhancement in conjunction with magnetic resonance (MR) imaging provides a means to evaluate tissue function, as well as morphology. Moreover, physiologic properties derived from kinetic analysis of dynamic contrast-enhanced data can improve the specificity of MR examinations. In this study, quantitative analysis of microvascular characteristics based on dynamic MR imaging were performed both for malignant and benign lesions using two types of contrast agents (CAs). A new MR macromolecular contrast medium (MMCM), 24 gadolinium-tetraazacyclododecanetetraacetic acid (DOTA)-dendrimer, was found to have a greater ability to distinguish benign from malignant lesions. When a blood pool agent was used, permeability differences in the two types of lesions were the most significant findings among all parameters considered.

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AFTER INTRAVENOUS INJECTION of the low-molecular-weight gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany), the vascular space is enhanced, but diffuses rapidly into the interstitial space.¹ Therefore, this kind of extracellular contrast agent (CA) has limitations in accessing vascularity and capillary permeability and cannot have high specificity for distinguishing benign lesions from malignant ones. On the other hand, gadolinium-tetraazacyclododecanetetraacetic acid (DOTA)-dendrimer (Gadomer-17; Schering), the prototype blood pool CA, is characterized by a prolonged diffusion process from the blood compartment into the interstitial compartment.²

The purpose of this study is to compare a new magnetic resonance (MR) macromolecular contrast medium (MMCM), gadolinium-DOTA-dendrimer, to a well-studied contrast medium, gadopentetate dimeglumine,³ for the potential of distinguishing benign from malignant lesions. For these types of contrast media and physiologic characteristics, variations in tissue physiology as defined by CA kinetics were displayed on an anatomic template, in a form easily interpreted by the physicians responsible for making differential diagnosis. These parametric maps of physiological tissue characteristics were obtained by pixel-by-pixel analysis of contrast-enhanced dynamic MR images.

MATERIALS AND METHODS

MR Imaging

MR imaging was performed on a Signa system (General Electric Medical Systems, Milwaukee, WI) operating at 1.5T. The system was equipped with a head coil. Animals were imaged in the prone position, and dynamic T1-weighted images were acquired with a fast spin echo sequence before, and at 1, 2, 3, 4, 5, 10, 15, 20, 25, 30 minutes after bolus injection. Imaging parameters were as follows: TR = 450 ms, TE = 16 ms, slice thickness = 7 mm, field of view = 15 cm × 15 cm, matrix = 256 × 128.

Animal Experiment Protocol

The experiments were performed in New Zealand white rabbits. Both abscess and VX2 carcinoma were experimentally induced in each thigh of the same animal. The VX2 carcinoma is an experimental tumor, developed from a squamous epithelium cancer of rabbit testicle. It is characterized by fast tumor growth and occurrence of central necrosis. Two types of CA (gadopen-tetate dimeglumine and 24 gadolinium-DOTA-dendrimer) were administered by manual bolus injection via the ear vein.

Data Analysis

To create the parametric map images, the acquired MR images were transferred to an IBM PC and analyzed using the language Matlab 5.3 (Mathworks, Inc, Natick, MA). The enhancement ratio determined by comparison of the pre- and post-contrast signal intensity was calculated for each time point. Then, the enhancement ratio-time curve in each pixel was reduced to a physiological parameter. The physiological parametric maps to be considered were maximum enhancement, time to peak, slope, highest enhancement rate, and permeability surface area (PS)-product per unit volume of tissue.

Capillary permeability was calculated from the concentration time curves of CAs in blood, $b(t)$, and in total region of interest, $c(t)$. From kinetic analysis of dynamic data, $c(t)$, in the early

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Fig 1. One of the contrast-enhanced dynamic MR images (left) and Patlak plot of the data in the selected ROI.

phase, is reduced to:

$$c(t) = \frac{K1}{V} \int_0^t b(t) dt + \phi_b b(t), \quad (1)$$

that is,

$$\frac{c(t)}{b(t)} = \frac{K1}{V} \frac{\int_0^t b(t) dt}{b(t)} + \phi_b. \quad (2)$$

Where, ϕ_b is the fractional vascular volume in the region of interest, and $K1/V$ is the mass transfer constant per unit volume ($\mu\text{m}/\text{min}/\text{mL}$), ie, PS-product per unit volume. Therefore, plotting $c(t)/b(t)$ versus $\int_0^t b(t) dt/b(t)$ results in a straight line of slope $K1/V$ in early phase. Figure 1 shows one of the contrast-enhanced dynamic MR images and the plot of $c(t)/b(t)$ versus $\int_0^t b(t) dt/b(t)$, so to speak Patlak plot,⁴ in the selected ROI. Differences in these physiologic parameters between abscess and VX2 carcinoma and between both CAs were analyzed.

RESULTS

Differences in the dynamic signal intensity changes after administration of CAs allowed the differentiation of normal, mild leaky and hyperpermeable microvessels. Even though most of parameters extracted from contrast-enhanced dynamic MR images showed higher values in both lesions when conventional micromolecular CA was used, the capability to distinguish benign from malignant lesion was prominent in a new blood pool contrast agent (Table 1). Permeability differences, when using a blood pool agent, in the two types of lesions were the most significant findings among all parameters considered (Fig 2).

DISCUSSION

From the parametric map analysis method of contrast-enhanced dynamic MR images, we could observe physiologic characteristics in a form easily interpreted on an anatomic template. As shown in Table 1, a new MR macromolecular contrast medium (MMCM), 24 gadolinium-DOTA-dendrimer, has a greater ability to distinguish benign from malignant lesions.

It is known that the endothelial integrity of microvessels is disrupted in malignant tumors.⁵ Among the considered parametric maps of physiological characteristics, vessel permeability maps reflected this property most effectively. Because

Table 1. Lesion Prominence in Abscess and VX2 Carcinoma

	Gadopentetate Dimeglumine		24 Gadolinium-DOTA-Dendrimer	
	Ratio of VX2 or Abscess to Normal Muscle	Ratio of VX2 to Abscess	Ratio of VX2 or Abscess to Normal Muscle	Ratio of VX2 to Abscess
Peak enhancement ratio				
VX2	1.459		1.568	
Abscess	1.388	1.051	1.157	1.355
Mean enhancement ratio				
VX2	1.350		1.471	
Abscess	1.280	1.055	1.104	1.332
Enhancement slope				
VX2	4.458		2.911	
Abscess	3.918	1.138	1.551	1.877
Permeability				
VX2	10.202		7.416	
Abscess	9.614	1.061	2.953	2.511

Fig 2. Vessel permeability maps. (Left) Gadomer-17; (right) Magnevist.

even benign lesions exhibit significant transcapillary leak of the small molecular CA, gadopentetate dimeglumine made it difficult to differentiate the two lesions statistically. On the other hand, when we used the macromolecular CA, the blood pool effect caused by the molecular size larger than the endothelial gaps in most of the tissues, made the malignant tumors look discriminative most prominently in the permeability map.

An essential prerequisite of this study was to obtain high-resolution images displaying vessels to find the concentration of blood, $b(t)$. However, no matter how we may obtain high-resolution images,

it is impossible to determine in a pixel the concentration contributed only by blood part. As an alternative, we assumed that the concentration $b(t)$ is the same as that in the femoral artery.

In conclusion, we are convinced that physiologic variables can be measured in an objective, reproducible, and noninvasive way, with appropriately good technique of MRI data collection and tracer modeling of the images. Moreover, lesion characterization using calculated vessel permeability map to new blood pool CA would contribute to reduce false positive diagnosis, and improve the specificity of MR examination.

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