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Water diffusion-exchange effect on the paramagnetic relaxation enhancement in off-resonance rotating frame

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Abstract

The off-resonance rotating frame technique based on the spin relaxation properties of off-resonance $T_{1\rho}$ can significantly increase the sensitivity of detecting paramagnetic labeling at high magnetic fields by MRI. However, the *in vivo* detectable dimension for labeled cell clusters/tissues in $T_{1\rho}$-weighted images is limited by the water diffusion-exchange between mesoscopic scale compartments. An experimental investigation of the effect of water diffusion-exchange between compartments on the paramagnetic relaxation enhancement of paramagnetic agent compartment is presented for *in vitro*/*in vivo* models. In these models, the size of paramagnetic agent compartment is comparable to the mean diffusion displacement of water molecules during the long RF pulses that are used to generate the off-resonance rotating frame. The three main objectives of this study were: (1) to qualitatively correlate the effect of water diffusion-exchange with the RF parameters of the long pulse and the rates of water diffusion, (2) to explore the effect of water diffusion-exchange on the paramagnetic relaxation enhancement *in vitro*, and (3) to demonstrate the paramagnetic relaxation enhancement *in vivo*. The *in vitro* models include the water permeable dialysis tubes or water permeable hollow fibers embedded in cross-linked proteins gels. The MWCO of the dialysis tubes was chosen from 0.1 to 15 kDa to control the water diffusion rate. Thin hollow fibers were chosen to provide sub-millimeter scale compartments for the paramagnetic agents. The *in vivo* model utilized the rat cerebral vasculatures as a paramagnetic agent compartment, and intravascular agents $(Gd\text{-}DTPA)_{30}$–BSA were administrated into the compartment via bolus injections. Both *in vitro* and *in vivo* results demonstrate that the paramagnetic relaxation enhancement is predominant in the $T_{1\rho}$-weighted image in the presence of water diffusion-exchange. The $T_{1\rho}$ contrast has substantially higher sensitivity than the conventional T_1 contrast in detecting paramagnetic agents, especially at low paramagnetic agent volumetric fractions, low paramagnetic agent concentrations, and low RF amplitudes. Short pulse duration, short pulse recycle delay and efficient paramagnetic relaxation can reduce the influence of water diffusion-exchange on the paramagnetic enhancement. This study paves the way for the design of off-resonance rotating experiments to detect labeled cell clusters/tissue compartments *in vivo* at a sub-millimeter scale.

Keywords: Off-resonance rotating frame; Paramagnetic relaxation enhancement; Diffusion-exchange effect; Volumetric coefficient; Imaging contrast; Rat brain images; Gadolinium chelates

1. Introduction

The paramagnetic relaxation enhancement in off-resonance rotating frame can increase the relaxivitiy and detection sensitivity of paramagnetic agents at magnetic fields higher than 3 T [1]. The enhanced relaxation rate constant depends on several factors, including the hydration number q, the rotational correlation time τ_R and the diffusion correlation time τ_D of T_1-type agents, and the nano-particles' diameter d of T_2-type agents [1,2]. These factors are critical to the smart labeling of molecular MR imaging. For instance, the alteration of hydration number reports the enzyme activations [3], the change of rotational correlation demonstrates the ligand binding [4,5], and the increase of relaxation rate indicates the DNA oliogmerizations [6].

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The off-resonance rotating frame technique can amplify the small difference in the relaxation rate constant, thus, enables the smart labeling strategy to become very efficient at high magnetic fields. In our previous paper, we have reported a novel method to quantify τ_R of T_1-type agents based on the paramagnetic relaxation enhancement effect in off-resonance rotating frame [2], where τ_R was extracted through the measurement of various residual z-magnetization profiles or difference magnetization profiles of water protons in off-resonance rotating frame. This method can be further extended to quantify the alterations of other factors such as q, τ_D and d, and to distinguish the small difference between the relaxation rate constants for T_1/T_2-type agents. Since the paramagnetic relaxation enhancement increases as the square of magnetic field strength [1], high sensitivity is expected for the detection of paramagnetic agents at high magnetic fields.

For the *in vivo* applications, the challenge arises from the interference of other relaxation pathways. In our previous paper, we have reported various methods used to quantify and suppress the contribution from the magnetization transfer pathway, and the strategies used to extract the dynamics of paramagnetic agents in the presence of a strong magnetization transfer effect [7]. However, biological systems are highly heterogeneous and contain numerous mesoscopic scale compartments in various tissues. Assuming that paramagnetic agents are restrained in a single compartment, water molecules can diffuse in/out of the influence region of paramagnetic agent molecules and exchange between different compartments via Brownian motion. Thus, the long off-resonance pulse, which is used to generate the effective field for off-resonance rotating frame, induces magnetization transfer inside tissue compartments [7] and allows water diffusion-exchange between different compartments. This raises an important and fundamental question for *in vivo* applications besides the magnetization transfer effect: how are the NMR signals affected by the water exchange between different compartments? Normally, the relaxation rate in the paramagnetic agent compartment is much higher than that in the tissue compartment (no paramagnetic agents). Thus, the diffusion-exchange between the tissue compartment and the paramagnetic agent compartment reduces the water relaxation rate for the paramagnetic agent compartment. This effect depends on the properties of compartment boundary. With water permeable membrane as the boundary, the effective diffusion distance is defined as $\bar{x} = \sqrt{6D_e t_m}$ for three-dimensional diffusion, where D_e is the effective diffusion constant, and t_m is the diffusion time window. For a membrane of δ thickness, the water permeability P_d is expressed as $P_d = D_e/\delta$. The time window for the diffusion-exchange, t_m, is determined by the off-resonance pulse duration τ,$t_m \sim \tau$. Since the water diffusion-exchange between compartments dilutes the apparent concentration of the paramagnetic agents in the paramagnetic agent compartment, the water relaxation rate for the paramagnetic agent compartment is expected to be reduced after a sufficiently long RF pulse is applied. A typical 25–500 ms pulse corresponds to a $\bar{x}$ of 10–50 μm at $D_e = 10^{-5}$ cm^2/s. For paramagnetic agents with compartment dimension l around a few millimeters, the water diffusion-exchange should not cause any serious problems because $l \gg \bar{x}$. For cell clusters, the compartment dimension may be comparable to the $\bar{x}$ since the size of cell is about 10–100 μm. Thus, the water diffusion-exchange is expected to affect the detection of paramagnetic agent labeled cell clusters. If the labeled cell clusters can be detected at a size smaller than 1 mm, most cancers then can be screened out at an early curable stage [8]. Therefore, the water diffusion-exchange effect for paramagnetic agents located in sub-millimeter compartments is extremely important for early detection of cancers. Here we are interested in how the NMR signal intensity for the paramagnetic agent compartment is altered by the diffusion-exchange effect, especially at low paramagnetic agent concentration with sub-millimeter compartment dimension.

Due to the effect of water diffusion-exchange, the NMR signal from paramagnetic agent compartment is mixed with those from other compartments. Extensive studies for a variety of situations have been carried out in the laboratory frame for T_1, T_2-weighted imaging, as shown in the comprehensive reviews elsewhere [9–14]. Theories based on the diffusion-Bloch equation were used to develop various models such as spatial distributions [10], two-site exchange [9–12,14], three sites exchange [12], and general moment expansion [13]. These studies used T_1-type paramagnetic agents [14–17] in order to evaluate blood volumes, blood vessel permeability, and perfusion *in vivo* [18–22]. The related parameters include the relaxation rate constant, the exchange rate constant and the population fraction for each compartment. Here, we only review the parameters and equations that are relevant to the models used in this paper. The compartment with T_1-type paramagnetic agents has a relaxation rate constant R_{1c}, and the compartment without paramagnetic agents has a relaxation rate constant R_{1nc}. Depending on the water exchange rate $1/\tau_e$ and the relaxation rate constant difference $R_{1c} - R_{1nc}$, there are three regions for the exchange kinetics: the fast exchange ($1/\tau_e \gg R_{1c} - R_{1nc}$), the intermediate exchange ($1/\tau_e \approx R_{1c} - R_{1nc}$), and the slow exchange ($1/\tau_e \ll R_{1c} - R_{1nc}$). For the membrane-separated compartments, $1/\tau_e$ is a function of water permeability P_d, membrane surface area S, and compartment volume V, $1/\tau_e = P_d S/V$ [11,12,17]. The fast or intermediate exchange kinetics will mix the NMR signals from different compartments, but the slow exchange will have a much less effect on the NMR signals. For the vasculatures *in vivo*, the intracellular/extra-cellular compartments of red blood cells are considered as one compartment due to the fast exchange kinetics. The red blood cells and plasma together form the intravascular compartment. The parenchymal cells with the interstitium form the extra-vascular compartment. The intra-vascular/extra-vascular compartments are considered as two compartments due to the slow exchange kinetics