Efficiency of Paramagnetic relaxation enhancement in off-resonance rotating frame

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Introduction

We have shown recently that the relaxivity loss for Gd-based MR contrast at high magnetic field (>3T) can be regained with the paramagnetic relaxation enhancement in off-resonance rotating frame (1). However, how the enhancement efficiency is related to the molecular structure of paramagnetic agents is unclear. We have derived a complete formalism for the relaxivity of Gd-based contrast agents in the off-resonance rotating frame at high magnetic field. Presented are the theoretical simulation and experimental validation for macromolecule conjugated Gd-DTPA.

Theory

For a macromolecule conjugated Gd-DTPA at high magnetic field where $\omega_s >> \omega_H >> \omega_e$ with T_{1M}, $T_{1\rho M} >> \tau_m$, the R_1 and $R_{1\rho}$ for the inner shell water can be simplified as follows,

$$R_{1,in} = Kc(3J(\omega_H)), \quad R_{1\rho,in} = Kc(2f_1(\theta)J(\omega_e) + 3f_2(\theta)J(\omega_H)) \qquad [1], [2]$$

Where K is a constant, c is the concentration of gadolinium, $f_1(\theta)=\sin^2\theta$, $f_2(\theta)=\sin^4(\theta/2)+\cos^4(\theta/2)$, $J(\omega)=\tau_c/(1+(\omega\tau_c)^2)$, θ is the tilt angle of off-resonance rotating frame, $\theta=tg^{-1}(\omega_1/\Delta)$. The $R_{1\rho}$ for the outer shell water is derived on the basis of Koenig's high field gadolinium model (2,3) as follows,

$$R_{1,out} = K'c\{7(1-(\alpha B_s^2(x)/2)J_{2OS}(\omega_s,\tau_{D,},\tau_{s2}) + 3[(1+\alpha)B_s^2(x)J_{1OS}(\omega_H,\tau_{D,},\tau_{s1\to\infty}) + (1-B_s^2(x))J_{1OS}(\omega_H,\tau_{D,},\tau_{s1})]\} \qquad [3]$$

$$R_{1\rho,out} = K'c[2f_1(\theta)(1+\alpha B_s^2(x))J_{1OS}(0)] + f_2(\theta)R_{1,out} \qquad [4]$$

Where K' is a constant, c is the concentration of gadolinium, J_{nOS} are the spectral density functions, Bs(x) is Brillouin function and $\alpha=(2S-1)/(2S+1)$. The total relaxation rate thus equals to $R_{1\rho}=R_{1\rho,in}+R_{1\rho,out}$. The experimental enhancement ratio can be extracted from the equilibrium residual z-magnetization according to $M(z)/M_0=\cos^2\theta R_1/R_{1\rho}$.

Methods

The parameters used in the mathematical simulation are as follows, τ_v=38ps, τ_{S0}=85ps, r_{e-H}=3.0Å, r=3.6Å, D=3.16X10^{-5} cm^2/s, τ_m=0.244μs, τ_R ranges from 80 ps for Gd-DTPA to 3000 ps, and the hydration water number q=1. BSA-$(Gd\text{-}DTPA)_{30}$, PLS-$(Gd\text{-}DTPA)_{32}$, Dendrimer-$(Gd\text{-}DTPA)_{40}$, Dextran-$(Gd\text{-}DTPA)_8$ were synthesized and characterized according to the methods reported elsewhere. All NMR experiments were carried with a volume coil on a 9.4 T Bruker Advance micro-imaging spectrometer. The off-resonance rotating frame magnetization profiles were obtained by applying a long pulse with a 5-60 kHz frequency offset followed by a 90° reading pulse. Residual magnetization was plotted as a function of frequency. The applied long off-resonance pulses were 500ms long with RF amplitudes of 2, 4 and 6 kHz.

Results and discussion

Fig.1(A) shows the relaxivity as a function of log(f) in laboratory frame, where f is proton Larmor frequency. With the typical parameters for Gd-DTPA(3), the overall correlation time τ_c is determined by the rotational correlation time τ_R for the Gd-DTPA unit, and the inner shell water dominates the contributions to the relaxivity enhancement at f<50 MHz. Fig.1(B) is the same relaxivity as a function of frequency at f>50 MHz, where all relaxivity enhancement disappears. Fig.1(c) is the rotating frame relaxivity as a function of frequency at the tilt angle θ=50°(i.e., ω_1=6 kHz, Δ=5 kHz), which demonstrates that there is τ_R-dependent relaxivity enhancement again. Fig.1(d) shows the enhancement ratio, $R_{1\rho}/R_1$, as a function of frequency, which increases as the square of the product $2\pi f\tau_c$. The value for the ratio can be as larger as 10 to 30 or more, depending on f and τ_c(or τ_R).

Fig.2 shows the measured enhancement ratio as a function of off-resonance frequency (Δ) with RF amplitude ($B_1=\omega_1/2\pi$) of 2, 4 and 6 kHz for four macromolecule conjugated Gd-DTPAs at 9.4 Tesla. The rotational correlation time for these Gd-DTPA units is known and has the order as: dextran ~ polylysine < BSA < dendrimner-g5. The measured enhancement ratio has the magnitude as dendrimer-g5 > BSA > polylysine > dextran. The highest $R_{1\rho}/R_1$ value for dendrimer-g5 is larger than 4, which corresponds to τ_R ~1500. These measurements show that very high relaxation enhancement efficiency can be achieved in the off-resonance rotating by altering the dynamics of the Gd-DTPA unit.

Conclusions

We have demonstrated that off-resonance rotating frame technique can substantially enhance the paramagnetic relaxation for T_1-type contrast agents at high magnetic field. (This work is supported by grant EB02912 from NIH).

References

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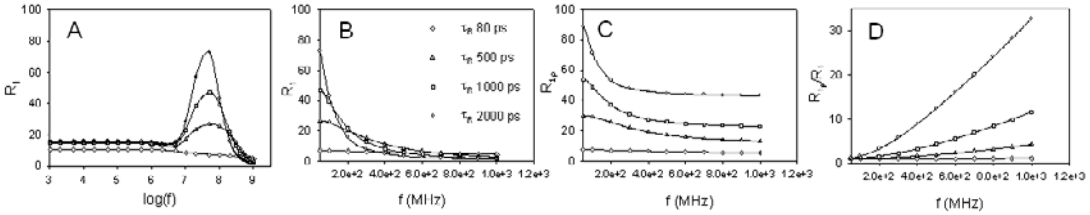

Fig.1 Simulated relaxivities and enhancement ratios.

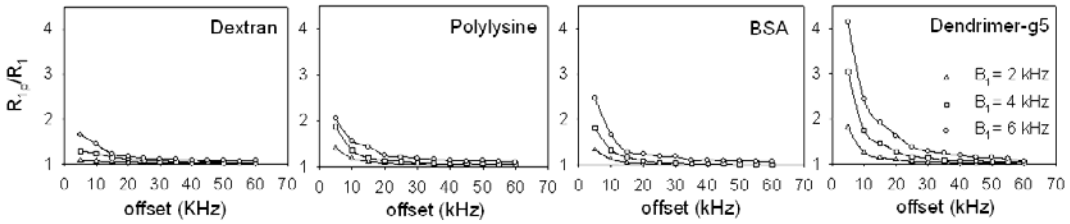

Fig.2 Measured enhancement ratios.