An estimate of Gd-DOTA diffusivity in blood by direct NMR diffusion measurement of its hydrodynamic analogue Ga-DOTA

Christian Wieseotte[1,2], Manfred Wagner[2], and Laura Schreiber[1]

[1]*Department of Radiology, Section of Medical Physics, Johannes Gutenberg University Medical Center, Mainz, Germany,* [2]*Max Planck Institute for Polymer Research, Mainz, Germany*

TARGETED AUDIENCE

Clinical Researchers, Physicists

PURPOSE

Contrast agent enhanced MRI is currently being used to quantitatively measure cardiovascular and cerebral perfusion [1, 2]. Calculations require precise knowledge of the applied contrast agent bolus shape, which is strongly influenced by the diffusivity of the contrast agent in blood[1]. Surprisingly, this fundamental property is still unknown. To our knowledge, only indirect estimates based on pharmacokinetic modeling of image intensities exist[3]. Therefore, the aim of this study was to investigate a different approach using hydrodynamic analogues to assess the diffusivity of Gd-DOTA.

METHODS

As the highly paramagnetic Gd^{3+} ion causes very fast signal relaxation, direct observation of the contrast agent complex by means of nuclear magnetic resonance is very difficult. The diffusion coefficient as described by the Stokes-Einstein equation depends on the temperature T, solvent viscosity η and hydrodynamic radius r of the molecule, which in this case is given by the DOTA chelator.

$$D = k_B T/(6\pi\,\eta\, r) \quad (1)$$

It is our hypothesis that substitution of the paramagnetic Gd^{3+} ion with ions of lesser magnetic moment increases the proton relaxation times while maintaining the diffusional properties of the complex. This method enables direct ^{1}H NMR diffusion measurements of the DOTA complex itself. Note that the difference in mass will only have a negligible influence on our results[4]. For our experiments we selected Ga^{3+} as substitute ion because Ga-DOTA is already used as a tracer in positron emission tomography (PET). Thus established methods for its synthesis are available. Successful chelation of Ga^{3+} was verified by ^{1}H NMR spectroscopy and MALDI-TOF mass spectroscopy.

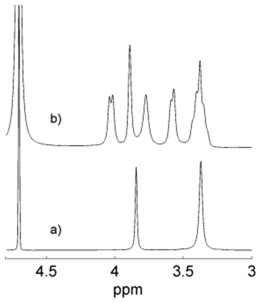

Figure 1: ^{1}H NMR spectra of a) pure DOTA and b) Ga-DOTA in D_2O

RESULTS

Our results show, that Ga^{3+} can be successfully incorporated into the DOTA cavity and allows for direct observation of the complex by means of ^{1}H NMR (Figure 1). The ^{1}H NMR spectrum shows five signal groups for Ga-DOTA whereas pure DOTA only showed two peaks. The splitting can be explained by a distortion of the planar DOTA geometry due to the metal incorporation, resulting in different chemical shifts for the individual proton sites. 2D DOSY experiments of the Ga-DOTA sample show a matching diffusion coefficient for all five signal groups (Figure 2). The averaged diffusion coefficient was calculated to be D = $4.38\,(0.04)\cdot 10^{-10}$ m^2s^{-1}. Although the complex ^{1}H signal background of blood prevents direct diffusion measurements, the diffusivity in human blood plasma can be calculated from the results in deuterated water by correcting for the higher solvent viscosity η (cf. Eq. 1). We calculated a diffusivity of Ga-DOTA in blood plasma at body temperature of D = 2.92 (0.25)·10^{-10} m^2s^{-1}.

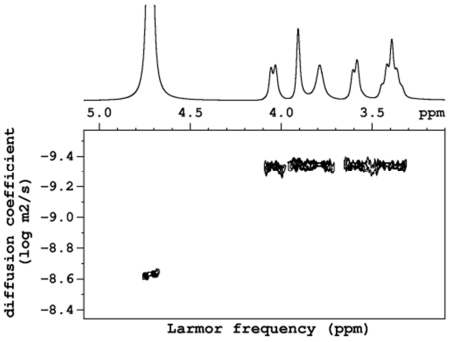

Figure 2: ^{1}H 2D DOSY NMR of Ga-DOTA in deuterated water at 310K

DISCUSSION

Due to similar hydrodynamic properties of Ga- and Gd-DOTA it appears safe to assume that their diffusional behavior is also similar. Therefore, our results for the PET tracer Ga-DOTA also apply to the MRI contrast agent Gd-DOTA. The estimated diffusivity of Ga-/Gd-DOTA reported in this study agrees with the previously reported value of 2.08 (0.88)·10^{-10} m^2s^{-1} which was estimated by analyzing contrast enhanced MRI images of necrotic tumor tissue[3].

CONCLUSION

The present study provides a directly measured diffusion coefficient of Ga-DOTA in deuterated water at 310K that is also valid for the MRI contrast agent Gd-DOTA. With the estimated diffusivity of both compounds in blood plasma, we hope to improve the precision of quantitative perfusion measurements and fluid dynamics simulations not only in the heart. Direct measurement of the diffusivity in blood plasma is still desirable to validate our method and remains subject to further studies.

ACKNOWLEDGMENT

Chemical support from Patricia Schiel is gratefully acknowledged as are helpful discussions with Janet Friedrich, Dr. Falk Dechent and Dr. Dirk Graafen.

REFERENCES

[1] Graafen D, Hamer J, et al., Quantitative myocardial perfusion magnetic resonance imaging: the impact of pulsatile flow on contrast agent bolus dispersion, Phys. Med. Biol., 2011; 56 (16): 5167-5185.

[2] Calamante F, Yim P J, et al., Estimation of bolus dispersion effects in perfusion MRI using image-based computational fluid dynamics, Neuroimage, 2003; 19 (2): 341-353.

[3] Koh T S, Hartono S, et al., In vivo measurement of gadolinium diffusivity by dynamic contrast-enhanced MRI: A preclinical study of human xenografts, Magn. Reson. Med., 2013; 69 (1): 269-276.

[4] Nuevo M J, Morales J J, et al., Mass Dependence of Isotope Self-Diffusion by Molecular Dynamics, Phys. Rev. E, 1995; 51 (3): 2026-2032.