Assessing the potential of Hexabrix as an ionic x-ray contrast agent to be used as an agent for chemical exchange saturation transfer (CEST) MR imaging at 3 T and 7 T

Benjamin Schmitt[1], Pavol Szomolanyi[2], Toshiyuki Shiomi[3], and Siegfried Trattnig[2]
[1]*Centre for High-Field MR, Medical University of Vienna, Vienna, Austria,* [2]*Medical University of Vienna,* [3]*Osaka University Graduate School of Medicine*

Introduction:

Chemical exchange saturation transfer (CEST) imaging has recently been shown to be a potential technique for targeted contrast-enhanced MR imaging via specially designed paramagnetic (PARACEST) or diamagnetic (DIACEST) agents [1]. The agents are usually designed to have optimized properties to provide strong CEST effects through exchangeable protons. Iopamidol, a contrast agent used in clinical computed tomography (CT), has also been introduced for use in MRI as a CEST agent [2], and initial experiments in animals [3] and humans [4] have been conducted.

This study was performed to evaluate if another clinically used ionic CT contrast agent, Hexabrix® (ioxaglate meglumine and ioxaglate sodium), provides characteristic MR properties to be used for CEST experiments at 3 or 7 T. Hexabrix® is a mixture of 39.3 % w/v ioxaglate meglumine and 19.6 % w/v ioxaglate sodium. Both molecules contain 4 amide protons and 2 hydroxyl protons, which may be subject to chemical exchange.

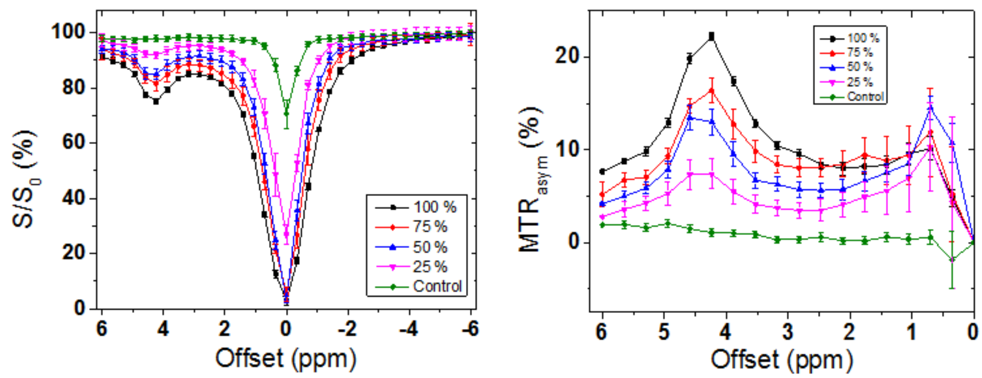

Fig. 1: z-spectra (left, S/S_0) and MTR asymmetry curves (right, MTR_{asym}) from ROI analysis of CEST images acquired at 7 T. The ROIs were placed in tubes with different concentrations of Hexabrix®, which are given in the inserts. Prominent CEST effects, which have a maximum at an offset frequency of 4.1 to 4.5 ppm from the water resonance, are apparent in all concentrations and absent in control. The maximum asymmetry shows a dependency on concentration of agent. Subtle CEST effects in the range of 0 to 1.5 ppm are obtained in all tubes with Hexabrix, but a dependency on agent concentration is not observed.

Materials & Methods:

Hexabrix® (Guerbet, France) 320 was used for MR experiments. It was diluted in physiologic sodium chloride solution and filled into tubes with a volume of 20 mL at concentrations 100 %, 75 %, 50 %, 25 %. One tube with pure NaCl solution served as a control. In-vitro experiments were conducted on a clinical 3 T MR System (Siemens Healthcare, Germany) using a standard 8-channel knee coil (InVivo, USA) and a whole-body 7 T MRI system (Siemens Healthcare) with a 32-channel head coil (Nova Medical, USA). CEST imaging was performed at 3 T and 7 T using a previously introduced 3D RF-spoiled gradient-echo (GRE) sequence [5]: Important imaging parameters at 3 T: T_E=3.29 ms, T_R=7.06 ms, resolution=0.6x0.6x3 mm³, matrix=176x256x16, acquisition time: 40 min. Imaging parameters at 7 T: T_E=3 ms, T_R=7 ms, resolution=0.8x0.8x2.9 mm³, matrix=144x192x16, acquisition time: 24 min. Selective RF presaturation was achieved using a series of 5 Gaussian RF-pulses with pulse duration τ_p=100 ms, interpulse delay τ_d=10 ms and a saturation continuous-wave amplitude equivalent (CWAE) of $B_{1\text{-}CWAE}$ = 2 µT at both field strengths. The first image series was recorded as a reference without RF presaturation (S_0) and 35 series were acquired with RF presaturation at offsets distributed equally from δ = –6 ppm to 6 ppm. Z-spectra from images were corrected for B_0 inhomogeneities on a pixel-by-pixel basis using a smoothing spline method. From corrected z-spectra, the asymmetry of the magnetization transfer rate (MTR) was determined by $MTR_{asym}(\delta) = MTR(+\delta)-MTR(-\delta)$.

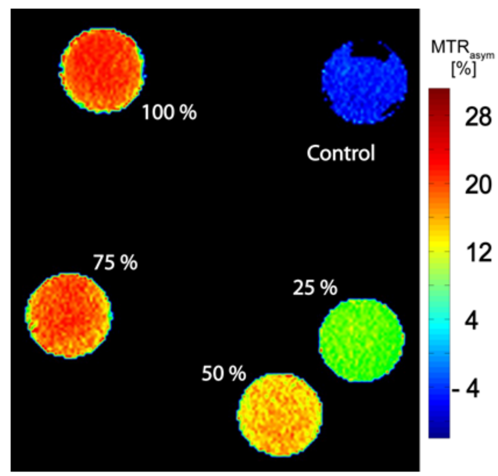

Fig. 2: CEST image from tubes filled with different concentrations of Hexabrix® acquired at B_0 = 3 T. The MTR_{asym} values at δ = 4.25 ppm were used as signal intensities and permit clear differentiation between tubes based on Hexabrix® concentrations. Numbers denote the concentration of Hexabrix in physiologic sodium chloride solution.

Results:

Z-spectra from CEST images acquired at 7 T show distinct MTR asymmetries between δ = 4.1 ppm to 4.5 ppm, which can be attributed to CEST effects (Fig. 1). The maximum MTR_{asym} of 22.25±0.48 % (mean±SD) was measured in pure Hexabrix® (Hex) at δ = 4.25 ppm. The maximum asymmetries at this offset frequency decrease with lower Hex concentration in tubes, i.e., 16.42±.36 % (75 % Hex), 13.02±1.36 % (50 % Hex), 7.43±1.49 % (25 % Hex), and are not visible in control. Further asymmetries are also visible at offsets closer to the water resonance between δ = 0 to 1.5 ppm. However, these effects show no obvious dependency on Hex concentration.

The results obtained at 3 T are in good qualitative agreement with those from 7 T, which means that prominent asymmetries with maxima between δ = 4.1 ppm to 4.5 ppm can be extracted from images at both field strengths. The dependency of asymmetry values on concentration in this range is also clearly detectable at 3 T. Thus, MTR_{asym} values at δ = 4.25 ppm can be used as signal intensities in CEST images to distinguish tubes with different Hex concentrations (Fig. 2). Absolute MTR_{asym} values at δ = 4.25 ppm measured at 3 T are slightly lower compared to the values obtained at 7 T, i.e., 20.56±0.74 % (100 % Hex), 15.02±1.56 % (75 % Hex), 12.22±1.61 % (50 % Hex), 5.82±1.74 % (25 % Hex).

Discussion and Conclusion:

The MTR asymmetries found between δ = 4.1 ppm to 4.5 ppm can be well attributed to CEST effects mediated by amide protons from Hexabrix ® molecules, which is emphasized by a clear dependence of MTR_{asym} values on agent concentration. The asymmetries observed at offsets closer to the water resonance may also be CEST effects, which occur due to chemically exchanging –OH protons of Hex molecules. However, these effects are too small to be resolved clearly, which may be caused by the low number of exchangeable hydroxyl protons in addition to fast exchange rates.

The results from this study clearly demonstrate that Hexabrix® can be used as a CEST agent. Being already clinically approved as contrast agent, it has the advantage that possible translations to different applications might be facilitated as long and costly procedures required for any new diagnostic product would be reduced. Since Hex is a ionic contrast agent, it could be used in vivo as a selective sensor for the concentration of various biomolecules that have a certain fixed charge density, such as glycosaminoglycans, which are components of cartilage tissue.

References: [1] Sherry AD & Woods M. Annu Rev Biomed Eng 2008; 10. [2] Aime S *et al.,* MRM 2005; 53(4). [3] Longo DL *et al.* MRM 2011; 65(1). [4] Keupp J *et al*. Proc. ISMRM 2011; 19: 828. [5] Schmitt *et al.* Radiology 2011; 260(1).