The influence of Holmium-166 loaded microspheres on ADC measurements using DWI

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Introduction: Diffusion-weighted imaging (DWI) is a powerful tool for the evaluation of radiation therapy since the apparent diffusion coefficient (ADC) provides information about tumor viability [1]. Problems may arise, however, when DWI is used in the presence of paramagnetic particles, e.g., to evaluate the effect of internal radiation therapy of liver tumors using Holmium-166 loaded microspheres (HoMS) [2]. In this case, the presence of HoMS invokes local non-linear gradients since the paramagnetic microspheres act like small dipoles. These local gradients add to the applied diffusion gradients but are not taken into account in the calculation of the ADC. For nanometer sized iron oxide particles, for which T2 signal decay is known to be strongly influenced by diffusion through local gradients, interference between local and applied gradients has been shown to result in an underestimation of ADC values, dependent on the concentration of the paramagnetic agent [3]. In previous work, we have shown that diffusion through local gradients is not only effective for nanometer particles, but also affects T2 (spin echo) decay for micrometer-sized particles [4]. Therefore it may be expected that ADC values will also be sensitive to the presence of micron-sized particles. In this work we aim to test this expectation and provide a basis to the interpretation of DWI in the presence of micrometer particles. This will be done by measuring the ADC of agarose gels containing various concentrations of HoMS, using a pulsed-gradient spin echo (PGSE) sequence with b-values ranging from 0–600ms/mm^2 .

Theory: In DWI usually a pulsed-gradient spin-echo sequence (PGSE) is used to measure the ADC. In this sequence a pair of (identical) linear gradients, characterized by the b-value, $b=(\gamma G\delta)^2(\Delta-\delta/3)$, is applied around the π-pulse of a standard spin-echo sequence. Here γ is the gyromagnetic ratio, G is the gradient strength, δ is the gradient duration and Δ is the center to center time of the two gradients. Dephasing of spins due to the first gradient will be counterbalanced by the second gradient for static spins, whereas for moving spins this will not be the case. This will lead to signal reduction dependent on the self diffusion coefficient of the material. Fitting the function $S(b)=S(0)exp(-b*ADC)$ to the signal intensities for each b-value provides a voxel based ADC. In a system containing HoMS, additional gradients induced by the dipole fields of the microspheres are present which add to the applied diffusion gradients. The individual dipole field is described by $B_{dipole}=\chi\cdot(R/r)^3\cdot(3\cos^2\theta - 1)\cdot B_0/3$, where χ is the volume susceptibility of Holmium, R is the radius of the microsphere while r and θ are spherical coordinates. To include the effect of the additional gradients on the ADC the function $S(b)$ must be extended to: $S(G) = S(0)exp(-b\cdot ADC-aG\cdot G_0)$ [3]. Here $S(G)$ (similar to $S(b)$) is the signal intensity at the echo time for diffusion gradient strength G, G_0 is the constant additional background gradient induced by the microspheres and $a = \gamma^2\delta D(\Delta-\delta/3)(TE-\Delta/2)$. Note that b itself is a function of G, $b(0) = G(0)$ and G_0 is actually a distribution of gradients $f(G_0)$. This expression indicates that echo attenuation is no longer linear dependent on diffusion gradient G^2, leading to an underestimation of the ADC if G_0 is not taken into account.

Materials and Methods: Phantoms: An agarose gel series (0.8% by weight) containing HoMS concentrations ranging from 0 to 5 mg/ml was made in 25-ml tubes. $MnCl_2.4H_2O$ was added to the native gel to decrease the baseline T_1 to reduce T1-weighting. The holmium content of the microspheres was 18.6% by weight resulting in a volume susceptibility of the microspheres of 880ppm (SI units) [5]. Experiments: ADC measurements of the gel series were performed on a 1.5-T clinical scanner (Phillips Healthcare, Best, The Netherlands) using a 2D diffusion-weighted spin echo sequence with b-values of 0,120, 240, 360, 480 and 600 ms/mm^2 and an effective echo time of 71ms (TR=2s, NSA=1, matrix=64^2, pixel size=2x2mm^2, slice thickness=10mm). Data analysis: Signal intensities of the MR images were measured for each b-value and concentration of HoMS. For each concentration, the ADC was obtained by fitting the function $S(b) = S(0)exp(-b\cdot ADC)$ to the signal intensities for each b-value, using a weighted least squares algorithm (Wolfram Mathematica 6.0). Resulting ADC values were linearly fitted.

Results: Signal intensities measured from the PGSE images for different b-values and for various concentrations of HoMS are plotted in fig 1, together with their (mono-exponentially) fitted function $S(b)=S(0)exp(-b\cdot ADC)$ (solid line). Clearly visible is the attenuation of the signal intensity due to the presence of HoMS, although a direct relation between HoMS concentration and signal intensity for a certain b-value was not found. The ADC for each concentration calculated from the fitting procedure is plotted in fig. 2. The baseline sample without HoMS has an ADC of 2.1 mm^2/ms which is close to the self-diffusion coefficient of water (2.3 mm^2/ms). Adding HoMS leads to a reduction of ADC where the reduction is linearly dependent on the concentration of the microspheres, as was also found for iron oxide particles[3]. Fitting the ADC's as a function of HoMS concentration gives a dependency of -0.1mm^2/ms per mg/ml HoMS

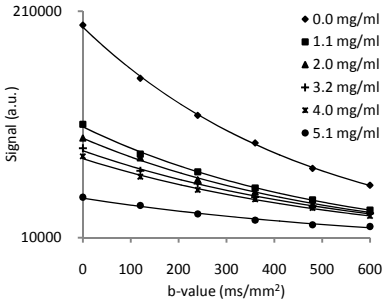

Fig 1. Signal intensities measured for various concentrations of HoMS in agarose gels for b-values ranging from 0-600 ms/mm^2. $S(b)=S_0exp(-b\cdot ADC)$ was fitted to the signal intensities and plotted (solid lines)

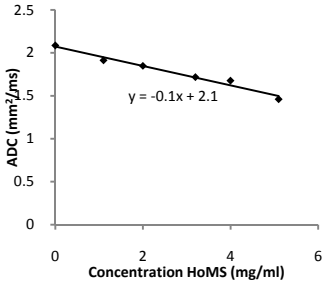

Fig 2. ADC values as determined from the fitting procedure. The ADC attenuation is linear with the concentration HoMS, where the slope of the linear fit is 0.1mm^2/ms per mg/ml HoMS.

Discussion and Conclusion: It was shown that the presence of HoMS attenuates the signal of diffusion weighted images leading to a ADC reduction of -0.1mm^2/ms per mg/ml HoMS. Apparently the effect of nanometer particles on ADC that was evaluated before [3] also applies to micrometer sized particles. The reduction of the ADC is caused by the additional gradients induced by the microspheres resulting in an additional weighting factor for calculation of the ADC which is not taken into account. Although the ADC behavior corresponds with our expectations, the signal intensities for the separate b-values are not completely understood. Signal intensities for a particular b-value should show a linear dependency on the concentration HoMS [4] which is clearly not the case. A possible explanation for this signal behavior is a global variation of the magnetic field over the field of view, leading to position dependent T2 decay. However this has still to be verified.
The dependency of the ADC on concentration HoMS is an effect that should be considered when using DWI for evaluating tumor viability after radioembolization. Since local concentrations of microspheres can range up to 15mg/ml, a potential underestimation of the ADC of 1.5mm^2/ms can occur which may lead to wrong diagnostic conclusions.

References: [1] JF Nijsen et al. *Radiology* 2004; **231**:491-499 [2] BJ Youn et al. *Acad Radiol* 2008; **15**:593-600 [3] J Zhong et al. *Journal of Magnetic Resonance* 1991; **95**, 267-280 [4] GH van de Maat et al. *Proc Int Soc Magn Reson Med* 2009; **17**:4468 [5] PR Seevinck et al. Magn Res Med 2008; **60**:1466-1476