Multi-echo spin-echo (MESE) signal behavior of paramagnetic Holmium-166 loaded microspheres for radiotherapy: experiment and simulation

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Introduction: Internal radiation therapy using Holmium-166 loaded microspheres (HoMS) has shown to be a promising technique for the treatment of liver metastases [1]. Due to their paramagnetic character, HoMS cause additional T_2* decay which can be used to quantify the amount of microspheres in the liver using gradient echo sequences [2]. However, for large concentrations of microspheres the signal decays too fast to be accurately sampled on a clinical MR scanner. An alternative approach can be provided by using a Carr-Purcel-Meiboom-Gill multi-echo spin echo (MESE) sequence to recover the signal for longer times. In this work we aim to explore the potential of MESE for quantification of HoMS, especially for high concentrations. To achieve this we will investigate the signal decay due to HoMS by experiments using HoMS suspended in aqueous solutions and by Monte Carlo simulations. The results will be compared with the model developed by Jensen and Chandra [3] in which they argue that additional signal decay due to the diffusion of protons through magnetic field inhomogeneities induced by paramagnetic objects in a MESE experiment can be modeled as $S(t) = \exp[-\alpha t^{3/8}]$ assuming Strong Field Behavior. Here, α depends on particle size r, volume fraction f, susceptibility difference $\Delta\chi$, diffusion coefficient D, field strength B_0 and echo spacing Δt. Since in this model α is directly proportional to the volume fraction of the particles, it would provide a tool for the quantification of HoMS.

Materials and Methods: Phantoms: An agarose gel series (0.8% by weight) containing HoMS concentrations ranging from 0 to 8 mg/ml was made in 25ml tubes. $MnCl_2.4H_2O$ was added to the native gel to decrease the baseline T2 to a value of ≈ 100ms to mimic blood. The holmium content of the microspheres was 18.6% by weight and the volume susceptibility of the microspheres was determined to be 880ppm (SI units) [2]. The diffusion coefficient of the native gel was measured to be $2\mu m^2/ms$ using diffusion weighted imaging. Simulations: Monte Carlo simulations were carried out as described by [4] using the next parameters: χ =880ppm, step size of the random walk = 0.01ms, total measuring time = 200ms, B_0 = 1.5T, number of iterations = 20.000, sphere radius = 15μm, Holmium density = 1.4g/ml. The signal magnitude was calculated at every 0.125ms using the phase information. Simulations were done for HoMS concentrations ranging from 1-25mg/ml and echo spacings varying from 10 to 22ms. Experiments: MESE measurements of the gel series were performed on a 1.5T clinical scanner (Phillips Medical Systems, Best, The Netherlands) using echo spacings ranging from 10 to 22ms (8 echoes, TR=2s, NSA=1, matrix=160^2, pixel size = $1x1mm^2$, FOV=$160mm^2$, slice thickness=12mm). Data Analysis: Signal intensities of the MR images for every odd echo were measured using a ROI of ±200 pixels and normalized to the intensities of the native gel. Corresponding signals from the simulations were also determined. The normalized signals were fitted to $S = \exp[-\alpha t^{3/8}]$ using a nonlinear regression algorithm (Wolfram Mathematica 6.0) from which α was calculated for the various concentrations of HoMS and echo spacings for both experiments and simulations.

Results: Signal intensities measured from the odd echoes of the MESE experiments for various concentrations of HoMS are plotted in fig. 1 on a logarithmic scale, together with the fitted functions $S(t) = \exp[-\alpha t^{3/8}]$ which provided α. Simulation results for the same echo spacing and concentration are also shown. From this figure it is clearly visible that both experiment and simulation are in good agreement with the theoretical curve S(t). Figure 2 shows α as a function of the HoMS concentrations for two different echo spacings as determined by the fit. Since α shows a linear dependency on the concentration, which is in agreement with [3], the results are linearly fitted and the slope C of the fit was calculated. For Δt=10ms, C is 0.034 for experimental data and 0.036 for the corresponding simulation. For Δt=16ms, C is 0.048 for experimental data and 0.050 for the corresponding simulation. In figure 3, α is plotted as a function of HoMS concentrations up to 25mg/ml as determined by simulations. Four echoes with Δt = 10ms were used to fit the data. For these data points C was calculated to be 0.033 which is in good correspondence to the calculated value of C for lower concentrations.

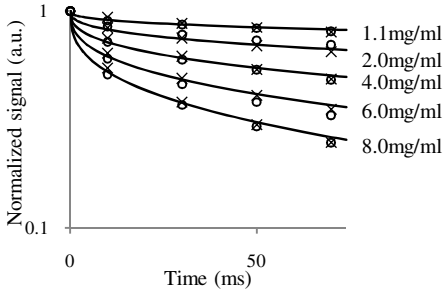

Fig 1. Logarithmic plot of the normalized signal decay for varying concentrations of HoMS. x: experiment; o: simulations; — function $S(t) = \exp[-\alpha t^{3/8}]$ fitted to experiments. Echo spacing Δt = 10ms

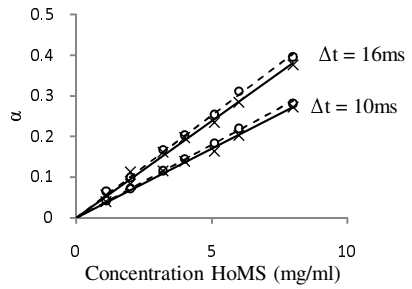

Fig 2. α as a function of the concentration of HoMS for Δt=10ms and 16ms as determined experimentally (x) and by simulation (o). Datapoints are linearly fitted (experiment: —, simulation: ---) from which a parameter C can be determined.

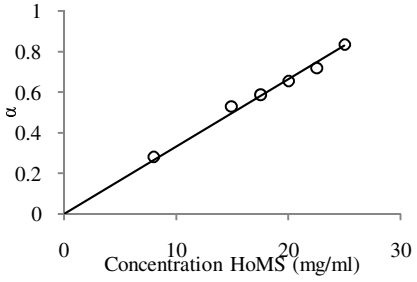

Fig 3. α as a function of the concentration of HoMS as determined by simulation for concentrations up to 25mg/ml. The line shows a linear fit with a slope C determined to be 0.033. 4 Echoes where used with Δt = 10ms

Discussion and Conclusion: Signal decay of HoMS containing systems as obtained from experimental data as well as from Monte Carlo are in good agreement with the theory of strong field behavior as proposed by [3] for MESE experiments. A small deviation for all the data series from $S(t)=\exp[\alpha t^{3/8}]$ is visible but this does not influence the dependency of the parameter α on the HoMS concentration since both experiment and simulation show the linear dependency of α on the HoMS concentration as expected from theory. We therefore believe that the model for Multi Echo Spin Echo decay of a system containing spherical magnetically heterogeneous objects as developed in [3] can be applied to systems containing HoMS. Since this theory gives a parameter α which is linearly dependent on the HoMS concentration, a good determination of the concentration of HoMS in the system under investigation can be obtained from fitting the data to S(t). Simulation shows that even for concentrations up to 25mg/ml the theory still applies. Some problems concerning minimum echo times which show up in T_2^* based calculations also show up in MESE measurements. Proper sampling of the T_2^* decay depends on the minimum gradient echo time (TE_{GE}) available on a MR scanner whereas proper sampling of the T_2 decay depends on the minimum available echo spacing (TE_{SE}). Although T_2 is much longer than T_2^*, the minimum TE_{SE} (>5ms) is also much longer than the minimum TE_{GE}. However, for very well defined signals, only 2 echoes are necessary to fit the data and determine α. In a clinical setting this might not be enough but using 4 echoes should be sufficient to find a good approximation of α as long as the signal to noise ratio of the last echo is high enough. In that case, HoMS could be determined up to a concentration of 20mg/ml, taking into account the apparent T_2 of the HoMS containing tissue (40-100ms) and α as determined from simulations

References: [1] JF Nijsen et al. *Radiology* 2004;231(2):491-499 [2] PR Seevinck et al. *Magn Reson Med* 2008; accepted 21 July 2008 [3] JH Jensen, R Chandra. *Magn Reson Med* 2000; 43:226-236 [4] Weisskoff RM et al. *Magn Reson Med* 1994; 31:601-610