Comparing different drug carriers for dynamic absolute MR thermometry

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Introduction Hyperthermia plays an important role in local drug delivery. Local temperature increase may induce local drug release from drug carriers [1] and may improve the extravasation of drug carriers [2]. However, there is a delicate balance between improving drug deposition in the tumor and causing thermal damage to the surrounding healthy tissue. MRI can be used to monitor dynamically the temperature *in vivo*. Several MR methods for performing thermometry have been proposed [3,4], however each method has its specific limitations, such as the ability to measure temperature changes only (requiring a known reference temperature) or low spatial and/or temporal resolutions. The multi Gradient Echo (mGE) method [5] allows for dynamic absolute temperature measurements based upon the proton resonance frequency shift (PRFS) of water with a high spatiotemporal resolution, but requires a temperature independent reference resonance frequency. Recently, it was proposed to use the temperature independent PRF of the ethylene oxide group of PEGylated liposomes as such a reference [6]. By doing so, the drug carrier may not only be used for transporting small drug molecules, but can be used at the same time for absolute MR thermometry. In this study we investigated in more detail the performance of different PEGylated liposome compositions and the applicability of several other drug carriers (polymeric micelles and HPMA polymers) as source for absolute dynamical temperature monitoring during hyperthermia facilitated drug delivery. **Materials & Methods** The following drug carriers were used in this study: i) 3 different compositions of DPPC: DSPE-PEG:Cholesterol liposomes (5% PEG-2000, 10% PEG-2000, 5% PEG-5000), ii) polymeric micelles (block copolymer of HPMA-Lac_n and PEG-5000) and iii) HPMA-Lac_n polymer. For each of these drug carriers the influence of temperature on the PRF of the hydroxyl group in water and a reference resonance frequency (in case of PEGylated drug carriers the ethylene oxide group in polyethylene glycol (PEG)) was first investigated using NMR spectroscopy (1D ^{1}H-NMR spectra were recorded on a Bruker Ultrashield 600 MHz spectrometer at 11 temperatures between 16 and 63° C. The drug carriers were either in NaCl solution or in serum 90% (v/v) and 10% D_2O. DSS (known amount, ~80 mM) was added as an internal chemical shift reference). In addition, the influence on the temperature measurements was investigated with respect to dilution of the samples and the pH. Finally, the accuracy and sensitivity of a multi gradient echo (mGE) sequence for temperature mapping were investigated on a dilution series using 5% PEG-5000 liposomes. MR imaging experiments were performed on a clinical 3-T whole body MR scanner (Achieva, Philips Healthcare, Best, The Netherlands) using a phantom consisting of a 25-ml boiling flask filled with liposome solution suspended in a 2000 ml beaker filled with manganese doped water. Spectrally selective attenuated inversion recovery (SPAIR) was used to achieve partial water suppression in the mGE sequence. Important scan parameters were: TR=500 ms, $TE_1/\Delta TE$=3.5/3.5 ms, 32 echoes, α=60°, Inversion Recovery delay = 200 ms, acquisition voxel size 2x2x8 mm^3, dynamic scan duration= 66 s. For all experiments, the frequency difference (Δf_{wPEG}) between the PRF of the ethylene oxide group in PEG (f_{PEG}) and the PRF of the hydroxyl group in water (f_w) was found by peak fitting in spectra constructed from the complex mGE signal. The temperature of the sample was verified with a calibrated fiberoptic thermometer (Luxtron). **Results** Figure 1a shows the temperature dependence of the frequency difference between the temperature dependent PRF of the hydroxyl group in water and the temperature independent PRF of the ethylene oxide group in the PEG, which is similar for both PEGylated liposomes as well as polymeric micelles. The temperature-induced shift of the hydroxyl group in water corresponded to 0.0093 ppm/°C. Figure 1b shows a linear relation between the amount of PEG present and the measured MR signal. The different liposome compositions generate an equal amount of signal per milligram of PEG incorporated in the liposome. In contrast the PEG in the polymeric micelles generate more signal per milligram PEG. Figure 1c shows temperature maps of a dilution series of 5% PEG-5000 liposomes. There is a clear increase in the standard deviation of the measured temperature at lower concentrations. HPMA polymers contain several temperature independent resonance frequencies. However, their NMR signal is lower than the NMR signal from PEG in liposomes or micelles (data not shown). **Conclusions** The principle of using the PEG group of drug carriers as temperature independent reference frequency for absolute MR thermometry is feasible. HPMA polymers contain several temperature independent resonances, however their signal is too low compared to the signal generated by PEG. Up to now micelles are the most promising drug carriers for performing absolute MR thermometry because they generate the highest signal per milligram PEG. The results from the dilution series with liposomes indicate that *in vivo* applications of mGE acquisitions in combination with intra venous injection lacks sensitivity. However, local application of the drug carrier (e.g. trans-arterial chemo embolization) or drug carriers optimized for PEG concentration may allow *in vivo* applications in the near future. **References** [1] De Smet, 2010, JCR [2] Kong [3] Ishihara, 1995, MRM [4] Kuroda, 2000, MRM [5] Sprinkhuizen, 2010, MRM [6] Deckers, 2010, ISMRM.

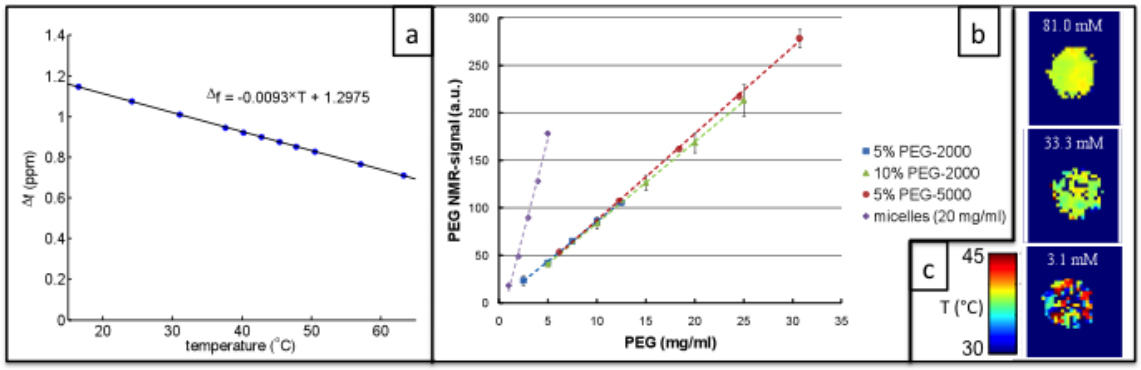

Figure 1: Relationship between the frequency difference (between the T-independent PRF of the ethylene oxide group in PEG and the T-dependent PRF of the hydroxyl group in water) and the temperature (a). Relationship between NMR signal and the amount of PEG in different drug carriers (b). Temperature maps of dilution series of liposomes (c).