New Thermosensitive Liposomes for MR-guided Hyperthermia

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Synopsis:

Newly designed long circulating liposomes are shown to be a temperature sensitive contrast agent for MRI when gadolinium chelate is trapped. At the therapeutic temperature of hyperthermia of 41°C nearly 50% of the gadolinium is set free, and can be detected by T1 changes in a MRI-Hyperthermia hybrid-system. Our results indicate that our new system has the potentiality to improve monitoring of hyperthermia and thus the therapeutic outcome. Moreover, the liposomes may also be used for specific release of chemotherapeutics by moderate hyperthermia.

Introduction:

Hyperthermia has proven to be an effective treatment concept for locally advanced deep-seated tumors (1,2). MRI could provide non-invasive temperature control of local hyperthermia (3,4). Reaching the therapeutic temperature slightly above 40°C is a crucial factor for the outcome of the hyperthermic tumor treatment (5). It has been show that paramagnetic liposomes may support MR thermometry (6). We demonstrate the feasibility of MR thermometry using new temperature sensitive long circulating liposomes with encapsulated gadolinium-chelate GdDTPA-BMA.

Material and methods:

LTSL were prepared by the lipid film hydration and extrusion method. Large unilamellar vesicles (LUV) were obtained by extrusion through nanopore filters of 200-nm pore size using a thermobarrel extruder at 60°C. Free GdDTPA-BMA was removed from the liposome suspension by dialysis (6). The relaxation time measurements were performed at 0.47 Tesla with a Minispec 120 (Bruker, Germany). For sample 1, relaxation times T1 were obtained by the inversion recovery method at a temperature range of 36 to 46°C. The time interval between the measurements was 15 minutes. The sample was again measured after 24 hours at 37°C. For reference a second (sample 2) and a third sample (sample 3) were measured at 37°C after previously incubation at 42°C for 15 minutes (sample 2) or incubation with triton/H2O to release all gadolinium (sample 3).

Results:

Figure 1 shows the changes of the relaxation time T1 for sample 1 in a sigmoid course between 108ms at 36°C and 18ms at 46°C with the center temperatures near 41°C. After cooling down T1 remains at a low value. Sample 2 shows the same T1 value as sample 1 at 42°C and sample 3 shows the same T1 value as sample 1 at 46°C.

Conclusion:

In the present study new designed long circulating Gd-liposomes were shown to be useful as contrast agent to monitor temperature in hyperthermia therapy. Detection of temperature dependent Gd-release of Gd-LTSL at 0.2 Tesla on a Magnetom Open Viva (Siemens, Germany) which is a part of MRI-hyperthermia hybrid-system. The same samples as used in the relaxation experiments were imaged at 20°C with a T1-weighted SE pulse sequence (TR=513ms/TE=30ms).

References:


Fig.1: Shortening of $T_1$ during temperature increase because of Gd-release from Gd-liposomes (0). The line shows a sigmoidal fit with center at about 41°C. Reference measurements at 37°C: $T_1$ measured 24 hours after the temperature scan (0), Gd-Liposomes incubated 15Min at 42°C ($\triangle$) and Gd-liposomes incubated with triton to release all gadolinium ($\nabla$).

Fig.2: The influence of Gd-liposomes on the intensity of $T_1$-weighted images. Sample 1: all Gd encapsulated in liposomes. Sample 2: partially release of Gd by incubation at 42°C for 15 minutes. Sample 3: full release of Gd by incubation with triton.