Simultaneous T1 and MR temperature monitoring in case of release of gadoteridol from thermosensitive liposomes during HIFU session

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Motivation: Temperature-induced drug delivery under MR image guidance offers a powerful method to study the spatiotemporal biodistribution of the locally induced delivery of the drug. A feasibility study was performed to monitor in near real-time the release of MR contrast agent loaded thermo-sensitive liposomes (TSL). For this, HIFU was used to induce a local temperature increase in a polyacrylamide gel containing TSL while dynamically acquired gradient echo images allowed simultaneously MR thermometry (Proton Resonance Frequency shift method) and T_1 mapping using the Look-Locker technique[1].

Materials and Methods: For this study, thermo-sensitive liposomes encapsulating 250 mM Gd-HPDO3A (Gd-TSL) were used[2]; the phase transition temperature of these TSL was found to take place at approximately 41.5°C, and the maximum release is achieved if TSL are exposed to a temperature of 42°C during 10 minutes.
Polyacrylamide gels were manufactured using the following composition: for a gel of 20 mL, 14.7 mL distilled water, 0.15 g NaCl, 5.0 mL acrylamide/bisacrylamide, 221 µL APS 10%, 1.5 µL Tetramethylethylenediamine were mixed. Addition of Silica (3%) ensured ultrasound absorption similar to *in vivo* tissue. During the gel fabrication, 1mL of Gd-TSL was added. Since the polymerization of the gel is an exothermic reaction, the gels were kept in a low temperature (5°C) water bath in order to prevent the undesired release of the Gd-HPDO3A from the TSL.
During the experiment, the Gd-TSL enriched gel was placed over a single element HIFU transducer (frequency = 1.5MHz, focal length=8cm; focal point has an elliptic shape of about 1 x 1 x 5 mm^3) and immersed in water maintained at 37.0 ± 0.5 °C (body temperature). The acquisition volume was positioned at the focal length; an EPI accelerated Look-Locker sequence was acquired dynamically using the following parameters: TE /TR / Flip angle (FA) = 18 ms / 37 ms /12°, FOV =64 x 64 mm, slice thickness = 6 mm; acquired pixel size = 1 mm x 1 mm; 26 inversion times were acquired every 6.2 sec (TI_0 = 23 ms, ΔTI = 51 ms).
20s after starting the MR acquisition, HIFU was applied at fixed power (10W during 2 minutes) in different gels. The data were processed (software RealTI - RtTech Bordeaux) using the detailed protocol described in Bos et al. consisting in each dynamic, for T1 mapping, fitting the recovery curve of the magnitude and for temperature mapping, the PRF evaluated on the computed dephasing evolving due to heating.

Results: Figure 1 shows that the temporal evolution of T_1 at different positions in the gel (heated or not heated region) is directly related to the temperature rise achieved at these positions after HIFU heating. As a consequence, at the focal point, a local decrease of T_1 parameter over time is noticeable as soon as the heating triggers the release of gadolinium when the phase transition temperature of Gd-HPDO3A is reached. Outside the focal point, T_1 remained stable since the temperature remained below the phase transition temperature of the TSL.

Discussion/Conclusion: This study demonstrates the feasibility to observe continuously the release of model drugs both spatially and temporally monitoring T1 and MR temperature variation simultaneously; Coupled with MR contrast agents, the evaluation of pharmacokinetic and pharmacodynamic (PKPD) parameters of such drugs could optimize *in vivo* drug delivery.

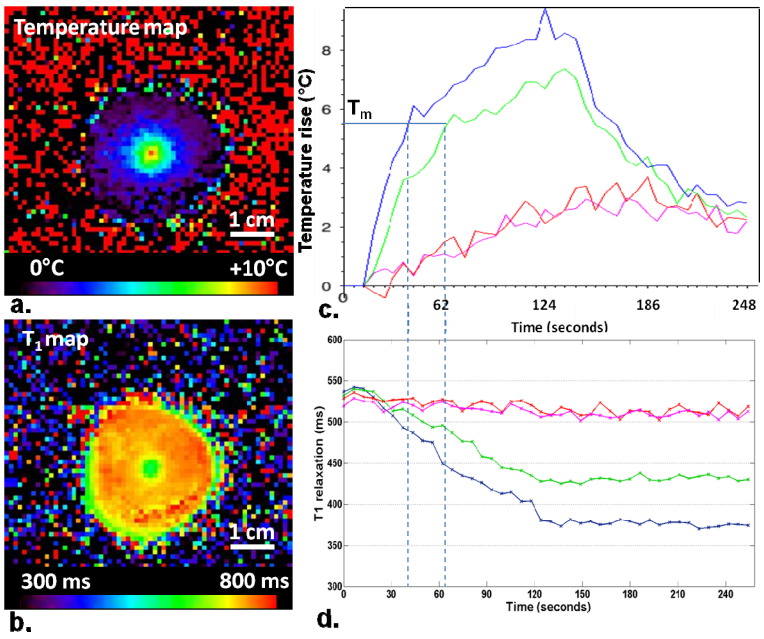

Figure 1: Typical MR temperature (**a.**) and associated T_1 maps (**b.**) at the end of the heating period; Temporal evolution of temperature (**c.**) and T_1 (**d.**) are also reported for four different heated or none heated pixels (blue in focal point, green: 2 mm far from the focal point, pink and red: 6 mm away from the focal point); Note that at the moment when the phase transition temperature (T_m=41.5°C) of the Gd-TSL is reached, the T_1 is identical in both heated positions. As the release increases with heating, T_1 decreases slowly.

References:
1. Bos C. et al., *Magnetic Resonance in Medicine* **54**, 1020-1024 (2005).
2. de Smet M. et al., *Journal of Controlled Release* **143**, 120–127 (2010).