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PURPOSE

Local drug delivery via localized hyperthermia-induced drug release from thermosensitive liposomes may reduce systemic toxicity of oncologic treatments, while maintaining or increasing efficacy. In addition to the drug, relaxivity contrast agents can be encapsulated which help visualize liposomal release using MR imaging. In this work, we present a fast dynamic MRI method to simultaneously monitor temperature, $T_2^*$, and $T_1$. The method is then used to assess the release of a clinically available gadolinium-chelate from Temperature Sensitive Liposomes (TSL) in an in vitro set-up.

MATERIALS & METHODS

Data acquisition (Fig. 1, sequences): All data was acquired on a 1.5 T MR system (Philips, Best, The Netherlands). Look-Locker acquisition: TR/T1/ATI = 4s/33ms/33ms, flip angle: 5°, 50 inversion times, TFE=5, voxel size=1×1×4mm³. Multi-echo SPGR sequences (ME-SPGR) were acquired using the following parameters: TR/TE=50/4.6/4.6ms, flyback gradient, flip angle α=25°, 10 echoes, voxel size=1×1×4mm³, dynamic scan time for 1 slice = 5.6 s.

Data analysis (Fig. 1, processing): An initial $T_1$ map was calculated from the Look-Locker data. Then, the phase changes were calculated on a voxel-by-voxel basis using the last echo phase image (TE=46 ms) from the Look-Locker sequence. The signal ratio of the $n$-th dynamic to the first dynamic for the ME-SPGR sequence is given by

$$S_n/S_0 = M_n(T_n)/M_0(T_0) = \frac{1 - e^{-\alpha T_n \Delta B_0}}{1 - e^{-\alpha T_0 \Delta B_0}} \left(1 - \cos(\alpha e^{-\alpha T_n \Delta B_0})\right)$$

(1).

The unknown effective proton density ratio $M_n(T_n)/M_0(T_0)$ effect was then estimated from the temperature variation ($T_0 - T_n$) using the Boltzmann equation. The second factor was estimated from the $T_2^*$ maps. $T_1$ was finally calculated iteratively from the signal ratio $S_n/S_0$, after accounting for changes in $M_0$ and $T_2^*$ and inserting the baseline $T_1$ from the Look-Locker. The last look locker sequence was used to validate the incremental $T_1$.

Experimental setup: TTSL loaded with Gd-HPDO3A were prepared (lipid ratio DPPC/DSPC/PEG2000-DSP/Cholesterol: 67/15/5/13) and monitored: phase transition temperature $T_m$=42±2°C (Differential Scanning Calorimetry) and diameter = 164 ± 2 nm (Dynamic Light Scattering). One sample containing fresh Gd-TTSL, the other samples consisted of preheated Gd-TTSL which served as control. In order to verify liposomal release, the samples were placed in a MR compatible water bath and heated from 38.6 to 46°C during 20 minutes of $T_1$, $T_2^*$, and temperature monitoring. A Luxtron (Santa Clara, CA, US) temperature optical probe provided independent temperature measurements.

RESULTS

A negative $T_1$ variation was observed in the Gd-TSSL sample after heating from 38.6°C until 42°C ($t = 11$ min), as shown in Fig. 3. During the phase transition (42°C) until 44°C (3 min), a sigmoidal-like decrease of $T_1$ was measured. Above the phase transition, $T_1$ values were similar to those of the control sample. Look Locker based $T_1$ measurements were found to match the final $T_1$ measurements that were calculated based on signal changes in the dynamic ME-SPGR data (Table 1), highlighting the need to correct for temperature $M_0$ dependence. A small $R_2^*$ change of 0.78 ± 0.18 s⁻¹ was observed. In additional ex vivo experiments using high intensity focused ultrasound and water bath muscle heating experiments (data not shown), similar results were obtained demonstrating the validity of the method.

DISCUSSION AND CONCLUSION

We presented a method that allows to obtain temperature, $T_2^*$ and $T_1$ information over time with a temporal resolution (5.6 s per slice) sufficient to monitor the release process in vitro (3 min). From 38.6°C, $T_1$ was observed to decrease proportionally with the temperature and by the fact with the water permeability of the liposomes. Complete release was confirmed by the similar $T_1$ values of the two samples after heating. The method will be an aid to monitor the release of MR-contrast agents from TSL in local drug delivery studies, as a correlate of the drug release.

REFERENCES


Figure 1: Summary of the acquisition (left) and the analysis (right) of the data over time.

<table>
<thead>
<tr>
<th>Method</th>
<th>TTSL</th>
<th>Preheated TTSL</th>
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</thead>
<tbody>
<tr>
<td>Look Locker</td>
<td>502 ± 14 ms</td>
<td>491 ± 10 ms</td>
</tr>
<tr>
<td>$M_0$ corrected</td>
<td>501 ± 17 ms</td>
<td>489 ± 14 ms</td>
</tr>
<tr>
<td>$M_0$ assumed constant</td>
<td>519 ± 17 ms</td>
<td>510 ± 19 ms</td>
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</tbody>
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Table 1: T1 values measured at the thermal equilibrium of 46.2±0.2°C.

Figure 2: $T_1$ vs. time (a.) and temperature (b.) of the TSL (black) and preheated TSL (blue). Upper right hand plots correspond to the probe temperature vs. time (left) and to the probe vs. the PRF-based temperature (right). Red and orange dots show the $T_1$ measurements from the Look Locker of TSL and the control, respectively.