Rapid Dynamic Temperature / T_1 / T_2* Assessment: A Method With Potential For Monitoring Drug Delivery.

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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[1]. 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/TI1/ΔTI = 4s/33ms/33ms, flip angle: 5°, 50 inversion times, TFE=5, voxel size=1×1×4mm^3. Multi-echo SPGR sequences (ME-SPGR) were acquired using the following parameters: TR/TE1/ΔTE=50/4.6/4.6ms, flyback gradient, flip angle α=25°, 10 echoes, voxel size=1×1×4mm^3, 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 images of the 3-slice ME-SPGR were used to estimate ΔB_0 using the method described by Dahnke H et al.[2] For the dynamic images, a T_2* map was estimated from an exponential fit to the multi-echo data. Temperature changes were calculated on a voxel-by-voxel basis using the last echo phase image (TE= 46 ms) using the proton-resonance frequency method[3]. The signal ratio of the n-th dynamic to the first dynamic for the ME-SPGR sequence is given by {1}. The unknown effective proton density ratio $M_0(T_n)/M_0(T_0)$ effect was then estimated[4] from the temperature variation $(T_n - T_0)$ using the Boltzmann equation. The second factor was estimated from the T_2* maps. ΔT_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.

$$\frac{S_n}{S_0} = \frac{M_0(T_n)}{M_0(T_0)} \cdot \frac{e^{-\frac{TE}{T_{2n}^*}}}{e^{-\frac{TE}{T_{2_0}^*}}} \cdot \frac{\left(1 - e^{-\frac{TR}{T_{1_0}+\Delta T_1}}\right) \Big/ \left(1 - cos(\alpha) e^{-\frac{TR}{T_{1_0}+\Delta T_1}}\right)}{\left(1 - e^{-\frac{TR}{T_{1_0}}}\right) \Big/ \left(1 - cos(\alpha) e^{-\frac{TR}{T_{1_0}}}\right)} \quad \{1\}$$

Experimental setup: TTSL loaded with Gd-HPDO3A were prepared (lipid ratio DPPC/DSPC/PEG2000-DSPE/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.

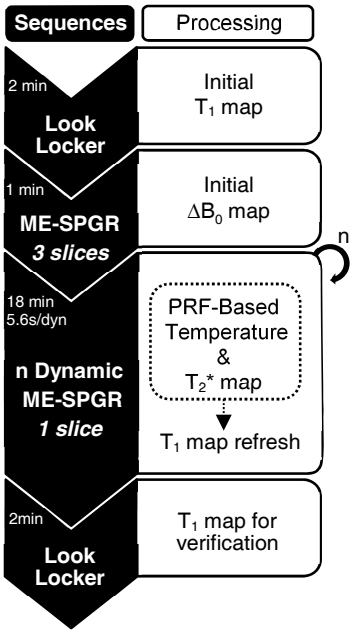

Figure 1: Summary of the acquisition (left) and the analysis (right) of the data over time.

RESULTS

A negative T_1 variation was observed in the Gd-TSL sample after heating from 38.6°C until 42°C (t = 11 min), as shown in Fig. 3. During the phase transition (42.2°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.

Method	TTSL	Preheated TTSL
Look Locker	502 ± 14 ms	491 ± 10 ms
M_o corrected	501 ± 17 ms	489 ± 14 ms
M_o assumed constant	519 ± 17 ms	510 ± 19 ms

Table 1:T1 values measured at the thermal equilibrium of 46.2±0.2°C.

DISCUSSION AND CONCLUSION

We presented a method that allows to obtain temperature, T_2* and T_1 information over time with a temporal resolution (5.6s 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.

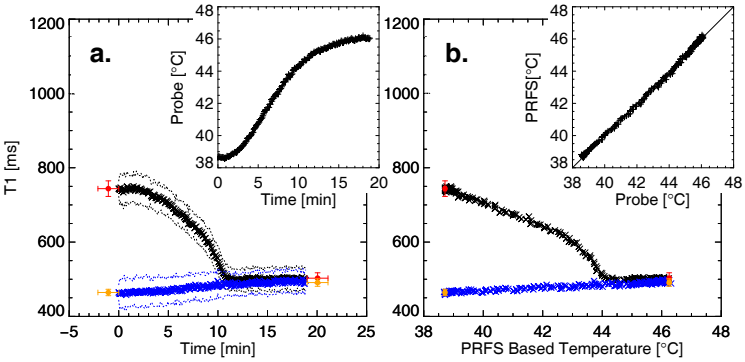

Figure 2: T1 vs. time (a.) and temperature (b.) of the TSL (black) and preheated TSL (blue). Upper right hand plots correspond to the probe temperature vs. time (left) and to the probe vs. the PRF-based temperature (right). Red and orange dots show the T1 measurements from the Look Locker of TSL and the control, respectively.

REFERENCES

1. De Smet M et al. *J Controlled Release.* 2010;143(1):120–127. **2.** Dahnke H et al. *MRM.* 2005;53(5):1202–1206. **3.** Poorter JD et al. *MRM.* 1995;33(1):74–81. **4.** Chen J et al. *JMRI.* 2006;23(3):430–434.