Rapid dynamic PRF/ΔT1/T2* monitoring for the characterization of heat-induced USPIO release from thermosensitive liposomes

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Introduction

Local drug delivery via encapsulation in thermosensitive magnetoliposomes (TSM) followed by localized heating-induced drug release may provide oncologic treatments with reduced systemic toxicity [1]. In addition to the drug, relaxivity contrast agents can be encapsulated and thus help visualize the release with simultaneous MR imaging [2]. In this work, we present a fast dynamic MRI method to simultaneously monitor temperature, T2*, and T1-changes. The method is then used to assess the USPIO release from TSM in an in-vitro experiment.

Material and Methods

Experimental setup: TSM (phase transition temperature Tm=43°C) loaded with USPIO were provided by Nanobiotix Laboratory (Paris, France). Three types of gels containing TSM, nonTSM and free USPIO, respectively, were inserted in a larger agar gel. Fig. 1a shows, in a coronal MR magnitude image, the spatial disposition of the three types of gels. Two monopolar RF electrodes were inserted on either side (Fig. 1a) and 30W of radiofrequency was applied for 16 minutes while performing dynamic MR imaging. Hardware notch filtering was used to eliminate all interference from the RF generator.

Data acquisition: All data was acquired on a 1.5 T MR system (Philips, Best, The Netherlands). Initial T1 values were measured with a Look-Locker acquisition. Then a dynamic series of magnitude and phase images was acquired with a multi-echo rf-spoiled gradient echo sequence (T1-FFE) including the following parameters: TR/TEfirst/ΔTE=80/3/3ms, flip angle α=15°, 6 echoes, voxel size=1.5×1.5×4mm^3, dynamic scan time for 3 slices = 5.3 s, total scan duration = 25 minutes. One point in the agar gel was monitored with a Luxtron (Santa Clara, CA, US) temperature optical probe (Fig. 1a) to provide the baseline temperature.

Data analysis:

The temperature evolution at each pixel was calculated using the last echo (TE=21ms) phase image with the proton-resonance frequency method. The multi-echo magnitude images were used to calculate T2*. T1 change (ΔT1) was calculated using the theoretical Ernst signal equation [3] for a T1-FFE pulse sequence, including T2* effects consecutive dynamics by iteratively dividing the signal for dynamic *n+1* by the signal for dynamic *n*. The unknown effective proton density M_0 is eliminated and ΔT1 is determined numerically, in an iterative fashion, from:

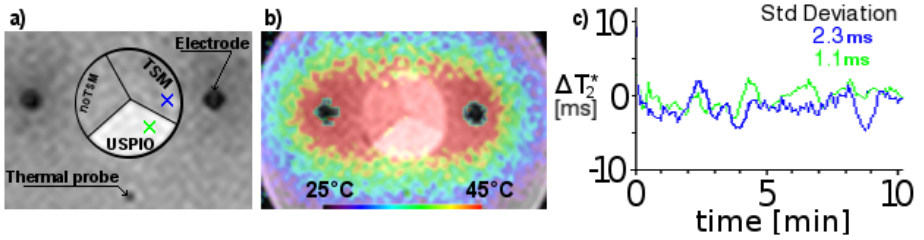

Fig. 1 a) Gel setup. b) Temperature after 10 min. of heating. c) ΔT2* evolution for pixels in Fig 1a.

$$\frac{\mathrm{Signal(n+1)}}{\mathrm{Signal(n)}} = \frac{M_0 e^{-\frac{TE}{T2^*_{n+1}}}\left(1-e^{-\frac{TR}{T1_n+\Delta T1}}\right)/\left(1-\cos(\alpha)e^{-\frac{TR}{T1_n+\Delta T1}}\right)}{M_0 e^{-\frac{TE}{T2^*_n}}\left(1-e^{-\frac{TR}{T1_n}}\right)/\left(1-\cos(\alpha)e^{-\frac{TR}{T1_n}}\right)}$$

The resulting ΔT1 curves were then empirically fitted with a sigmoidal function using a Marquard-Levenberg algorithm. The sigmoid is determined by three constants: the difference in amplitude between the start and end values of the sigmoid (ΔT1), the highest value of the slope of the sigmoid (the "velocity" V) and the time to the point of highest slope (τ). As the release process is complete when the sigmoid reaches its end value, τ represents the "half-time" of the release process.

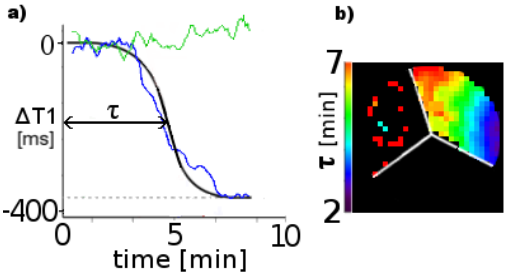

Fig. 2 a) ΔT1 for pixels in Fig1a. b) Half-time map

Results

The absolute temperature map obtained after 15 minutes of heating is shown in Fig. 1b. The temperature evolution indicated that both the TSM gel and the nonTSM gel were exposed to Tm or higher for at least 5 minutes. No T2* variation could be observed in either of the three regions during heating, as shown in Figure 1c.

A reduction of T1 occurred in the TSM region, whereas the NonTSM and free USPIO gel regions used as control showed an increase of T1 following temperature variation (Fig. 2a). The baseline T1 for the TSM region was 812 +/- 27 ms, and the average ΔT1 for the TSM region was -339 +/- 82 ms, corresponding to a reduction of 41%. The half-time (τ) map for TSM (Fig. 2b) shows that the T1 decrease takes place with increasing latency at larger distance from the electrodes. The distribution of temperatures corresponding to the half-times of each voxel is given in Fig. 3

Discussion

We presented a method that allows to obtain temperature, T2* and T1 kinetic information with a temporal resolution sufficient to monitor the release process in-vitro.

MR thermometry confirmed that the release conditions were met for the three gel samples.

The lack of T2* variation suggests that the USPIO concentration / distribution per voxel remains constant in the three types of gel. The ΔT1 variation, however, in the TSM region was significant. The statistical distribution of half-time temperatures is specific to this experiment, but it could be used more generally to characterize the TSM release process.

The future step is to perform in-vivo experiments, and in this context monitoring the T2* has two reasons: to monitor the change of USPIO concentration/voxel at the arrival of the TSM bolus, and then update the T2* values for correct ΔT1 monitoring of the heat-induced release.

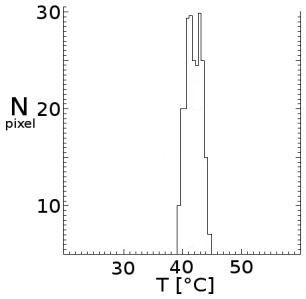

Fig. 3 Temperature distribution at the half-time at each voxel of the TSM region
Mean = 41.2 +/- 2.7 °C

Acknowledgement

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References

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