Simultaneous Monitoring of Temperature and R_1: Methods and Preliminary Results of Application to Heating of Thermosensitive Paramagnetic Liposomes

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Introduction

Magnetic resonance imaging can provide tomographic temperature maps non-invasively. Therefore, MR thermometry can have utility for controlling hyperthermia aimed at liberating drugs from thermosensitive liposomes (1). The lipid bilayer of these liposomes switches to a permeable state when temperature increases above its transition temperature. Incorporating an MR contrast agent in the liposome will increase the R_1 ($\equiv 1/T_1$) when the liposomes become permeable, which would permit a radiological control of the drug being released using MR-imaging (2,3). This approach to local drug delivery may benefit from a method to simultaneously monitor temperature and R_1.

To this end, we use the complex nature of the MR signal. With the proton resonance frequency (PRF) method (4), temperature changes are accessible through the phase of the signal. R_1 is encoded in the magnitude of the signal (5). The feasibility of fast combined R_1 and temperature mapping using a Look-Locker EPI sequence will be demonstrated *in vitro* for a preparation of thermally sensitive liposomes that is heated using an RF system.

Materials and Methods

MR Imaging: Experiments were performed on a 1.5-T scanner (Gyroscan Intera, Philips, Best). Serial segmented Look-Locker EPI (LL-EPI) images were aquired in 4 shots (slice thickness 8-mm, field of view 256×192 mm^2, matrix 128×92). A shot consited of a non-selective inversion followed by 20 excitation pulses of 12º, 40.4 ms apart, to sample the recovery curve and a delay of 1200 ms, leading to an acquisition time of 8 seconds. Echo time was 18 ms. Inversion recovery spin echo experiments with different inversion delays (50,100,150,200,300,500,800,1250 and 1800 ms) provided R_1 reference values. A quadrature neck coil was used for signal reception.

Image analysis: Scripts for on the fly evaluation of temperature and R_1 from real and imaginary data were written in IDL. Real and imaginary images for all 20 timepoints on the recovery curve were available for evaluation directly after acquisition.

R_1 was calculated using the well-described Look-Locker method (5). For analysis, complex data were converted to signed magnitude data by using the available phase information. A least-squares fit of the form a-b Exp[-c] provided R_1^*, from which R_1 was obtained after correction for the excitation pulses.

The PRF method for MR-thermometry allows to calculate temperature changes ΔT from changes in signal phase Δφ, using the relation $\Delta T = \Delta\varphi / c\ \gamma\ TE\ B_0$ with γ the gyromagnetic ratio, TE the echo time, B_0 the magnetic field, and c the temperature dependent chemical shift of approximately -0.01 ppm/ºC. For evaluation of Δφ, phase information from all timepoints along the recovery curve is used. To this end, we make a scatterplot in the complex plane of the correlations $C_{n,t}$ (Fig. 1)

$$C_{n,t} = \frac{S_{n,t} S^*_{n,t_0}}{\sqrt{S_{n,t} S^*_{n,t} + S_{n,t_0} S^*_{n,t_0}}}$$

for all n, where "t" and "t_0" refer to the dataset under evaluation and the reference dataset, respectively. S^* denotes the complex conjugate; the phase of SS^* is equal to the phase difference between S and S^*. Then, Δφ is obtained from a *perpendicular* least-squares fit through the origin $y = bx$, where $x_n = \mathrm{Re}(C_{n,t})$ and $y_n = \mathrm{Im}(C_{n,t})$.

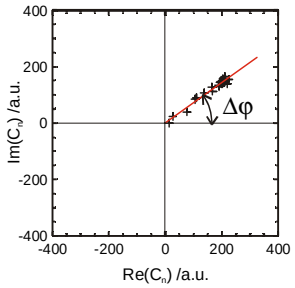

Figure 1: Data from the cooling experiment (ΔT = -9.7ºC). A prependicular fit (line) to the correlations C_n provides Δφ, and allows temperature calculation.

Experiments: Accuracy of R_1 and precision of R_1 and Δφ of the LL-EPI technique were assessed in tubes with different Gd-DTPA concentrations. Phase precision obtained by integrating the information of the whole recovery curve was compared to phase precision obtained from the data point with maximum absolute value. Accuracy of MR-thermometry using the LL-EPI method was tested by monitoring cooling of warm agar gel. Thermocouple readouts served as the gold-standard. Finally, an agar gel (1 % w/w) doped with 0.5 mM Gd-DTPA and NaCl (1 % w/w) was prepared containing liposomes with a transition temperature of 57ºC encapsulating 174 mM Gd-DTPA-BMA (gift of Nycomed Amersham). In the gel, effective concentration of Gd-DTPA-BMA contained in liposomes was 1.2 mM. The sample was heated by RF-needles 3 cm apart applying 25 W RF-power, while temperature was monitored using MRI.

Results

R_1 measurements were accurate within 5% or better and had a precision of 7% or better for R_1 > 1.5 /s. Precision of the temperature measurement was 0.13ºC or better for the tubes with R_1 > 1.5 /s. The tubes with lower R_1 had a lower precision of 0.22ºC. Integrating the phase information of all points on the recovery curve led (in this case) to a gain of a factor 2.5 (range 2.2-3.8, P=0.0002, paired t-test). The cooling experiment showed a good correspondence between thermocouple readouts and MR-thermometry using the LL-EPI sequence. R_1 of the gel depended linearly on temperature: dR_1/dT = -0.11 /s/ºC, r^2 = 0.92. RF-heating of a gel with thermosensitive liposomes showed at low temperatures a linear decrease of R_1, and then at temperatures above 50ºC, a strong, reversible increase of R_1 with temperature, cf. Ref 2 (Fig.3). Near the needles a permanent R_1 increase was observed.

Discussion

These experiments demonstrated the feasibility of simultaneous mapping of temperature and R_1 in near-real-time. Combining both measurements in the same sequence implies a trade-off of acquisition time, and R_1 and temperature precision, but in general an effective temperature precision (<0.5ºC) is easier to obtain than an effective R_1 precision (<<5%). Preliminary results indicate that monitoring of liposome permeability during MR-controlled heating is feasible.

References

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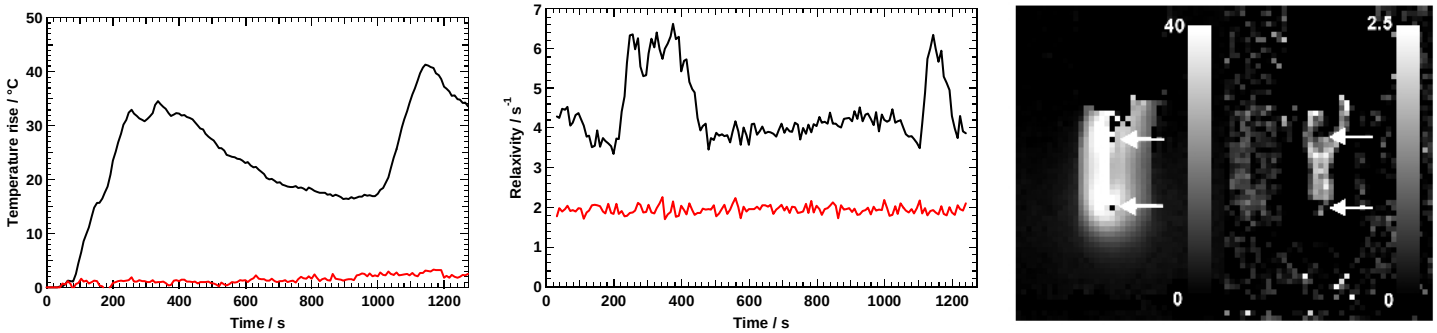

Figure 2: Temperature rise with respect to room temperature (22ºC) (left) and R_1 (middle) in a heated point in the tube containing liposomes (black), and in a control tube without liposomes (red). Two cycles of heating were applied. Temperature rise (ºC) and corresponding R_1 change (s^{-1}). (right) Arrows indicate RF-needle positions. During the previous heating session, R_1 in the region at the lower needle had already permanently changed.